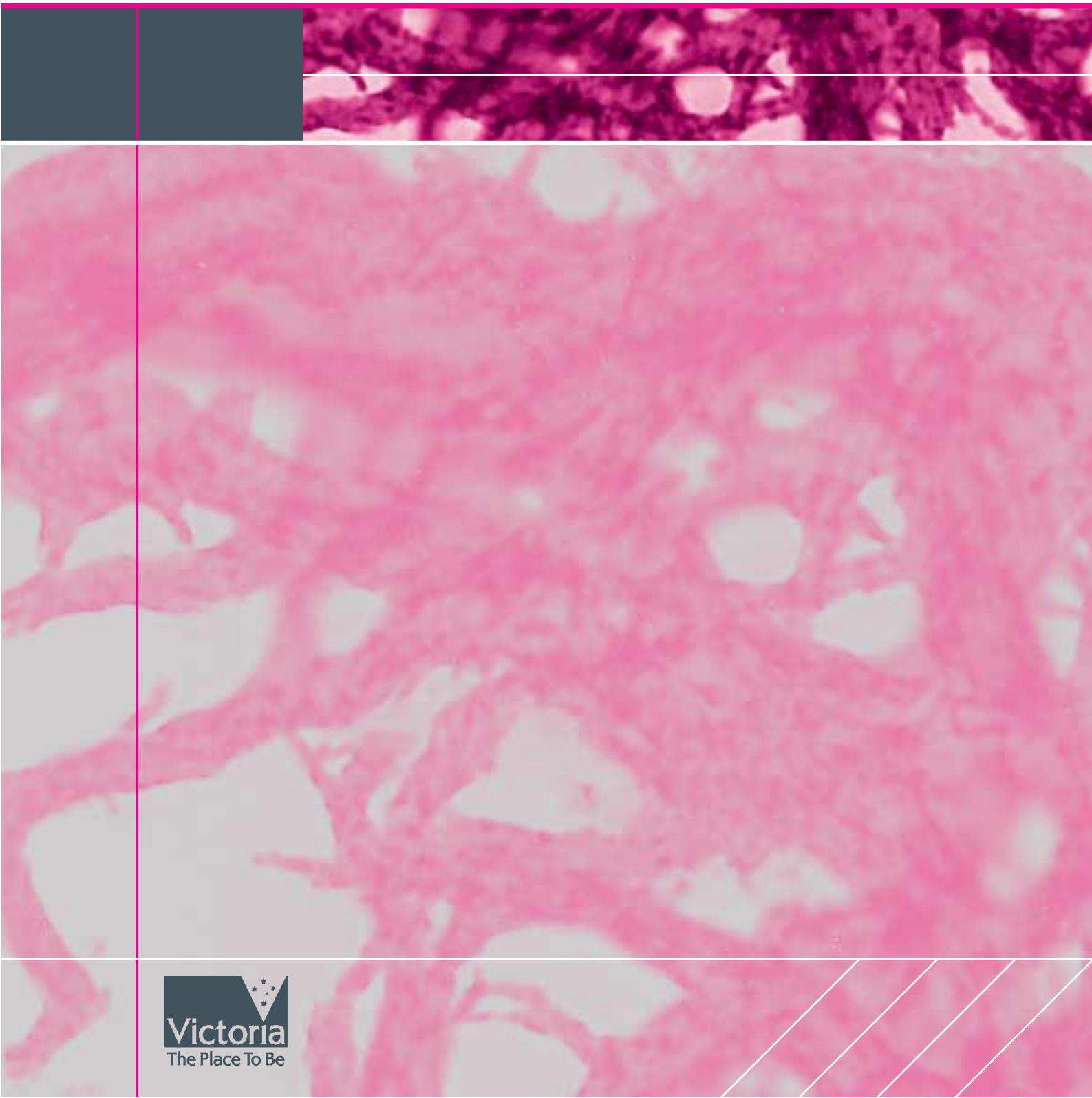
Management, Control and Prevention of Tuberculosis

Guidelines for Health Care Providers (2002–2005)



Victoria
The Place To Be

Management, Control and Prevention of Tuberculosis

Guidelines for Health Care Providers (2002–2005)

Department of Human Services

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Disclaimer

These guidelines have been prepared following consultation with experts in the field of infectious and respiratory diseases, occupational health and safety regulations and infection control practices, and are based on information available at the time of their preparation.

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Foreword

In 1993, the World Health Organisation declared tuberculosis (TB) to be a global emergency. The situation remains largely unchanged, with an estimated 8.42 million new cases in 1999 and the global incidence rate projected to rise by 3 per cent per year to a total of 10.2 million cases by 2005. Only in industrialised countries is the number of cases expected to fall (down by 2–3 per cent per year).

In 1994, the then Department of Health and Community Services developed key initiatives in recognition of the changing epidemiology of TB. It produced the document Eliminating Tuberculosis: A Strategy for Victoria to identify and target groups at increased risk of TB, and to address issues such as delays in diagnosis and the risk of multidrug-resistant TB emerging in the community. The publication of *Management, Control and Prevention of Tuberculosis—Guidelines for Health Care Providers* in 1995 was an integral part of that strategy.

The guidelines, for general practitioners and other clinicians, were developed along with general education and awareness programs for high risk groups. It is essential that health professionals are aware of the increased risk of TB in some community groups, such as those born overseas, the aged, the homeless and residents of prisons and other settings. The guidelines were compiled to support professional and institutional practices in protecting health care workers and students in hospitals and health care settings, and preventing nosocomial transmission of infection and disease.

In May 2000, the Department of Human Services decided to review and update the original guidelines. This review was prompted by the outcomes of the Melbourne Mantoux Study (completed in 1999), which found that health care workers were significantly more likely than non-health care workers to have positive tuberculin skin tests. The study authors made recommendations about infection control practices, surveillance and education.

A working party consisting of specialist infectious diseases and respiratory physicians, a representative of the Australian Nursing Federation and Department of Human Services staff was convened to update the 1995 guidelines. The aim was to include new issues that had arisen since the original publication and clarify areas that the previous guidelines had not properly covered. The revised document was expected to be evidence based or based on consensus, and aimed at public health practitioners, general practitioners and health care facility staff.

Chapters on the hospital care of active TB and the prevention of infection in health care workers have been significantly revised and expanded. They will assist individual institutions in developing policy and practices that are appropriate to effective TB control in their particular setting. New chapters cover airline travel, migrant screening and the supervision of treatment, while the chapters on TB in special situations (such as HIV co-infection and pregnancy) have been updated to reflect contemporary practices, both in Australia and overseas. Care has been taken to ensure recommendations are consistent with other current Department publications, including guidelines for the classification and design of isolation rooms and for the immunisation of health care workers.

As the prevalence of TB in the Australian-born community continues to decline, health professionals must maintain a high index of suspicion for TB when a patient seeks health advice for symptoms consistent with TB disease, particularly if the patient belongs to an identified high risk group. These revised guidelines will remain instrumental in heightening that awareness and assisting the goal of eliminating TB in Victoria.

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Contents

1. Introduction

In contrast with the current world situation, Australia is fortunate in having a low but relatively constant pattern of tuberculosis (TB). This is due predominantly to the reactivation of latent infection in people who were previously infected in their countries of birth or during their childhood in Australia when community TB rates were much higher. The incidence of TB in Australia averages around 1000 new cases per year (in Victoria, 250–320 per year). Approximately 85 per cent of TB notifications occur in people born overseas, with 50 per cent of these cases occurring in the first five years of residence in Australia. There is evidence of only a low level of person-to-person transmission within Australia, mainly in specified risk groups, as shown by DNA fingerprinting studies, that only occasionally demonstrate similar patterns in cases that may be associated. Active TB, therefore, 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, migration, relocation and/or family disruption.

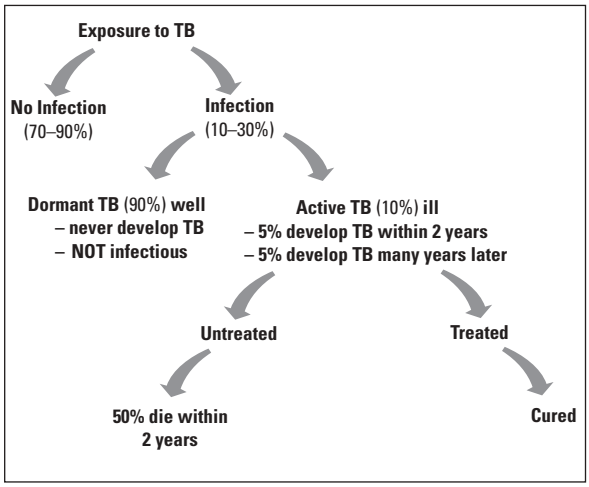
Mycobacterium tuberculosis and the other members of the *M. tuberculosis* complex—*M. bovis*, *M. africanum* and *M. microti*—are parasites of the pulmonary macrophage. Once infected droplet nuclei are inhaled and deposited on the bronchial mucosa, the organisms are ingested by macrophages and transported 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; rather the organisms are able to inhibit the phagocytic process, and thus replicate within the macrophages whilst being transported to regional lymph nodes or the pleura.

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

In most exposed people, however, the pulmonary macrophages remain contained at the site of infection and in the local regional lymph nodes. As a result, a primary granulomatous lesion (Gohn's focus) develops, including a local area of pneumonitis and swelling of regional lymph nodes, healing by resolution, scarring, and the eventual deposit of calcium within the scar tissues. Residual infected macrophages can be identified within this scar tissue, containing bacilli that have gone into a state of 'dormancy' or latency and that are maintained in this state by the individual's normal cell-mediated immunity. This state of latency can last for many decades, often until the death of the host (unless some event impairs the cell-mediated defence mechanisms). This ability of *M. tuberculosis* to change its metabolic state to dormancy over many decades accounts for the persistence of the organism within the macrophage environment, and for the potential for reactivation at any time, resulting in possible transmission to other individuals.

When cell-mediated defence mechanisms are impaired, the bacilli may become metabolically active again, replicate and move outside the macrophage into the surrounding tissues. This is known as 'reactivation', which is the usual pattern of disease development in most cases of active TB in our community. In general terms, only 5-10 per cent of all those who have been infected with TB develop active disease, with the greatest period of risk being in the first two years after infection (Figure 1).

Figure 1: The Natural History of TB Infection



The advent of HIV co-infection has dramatically changed the world TB situation, transforming a 5–10 per cent lifetime risk of reactivation of latent infection into a 10 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.

TB, 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 may be in compromised situations— for example, a person who is aged, diabetic, on steroid therapy or immunosuppressed— and who presents with cough, weight loss, sweats, general ill health, unusual pneumonias or infections and so on. Such people should be investigated accordingly. In short, **THINK TB**.

For advice regarding clinical presentation and investigative techniques not covered in these guidelines, refer to standard texts on TB or infectious diseases.

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2. Tuberculin Testing

2.1 Introduction

The tuberculin skin test (TST) is currently the only readily available method for identifying latent infection with *M. tuberculosis*. Tuberculin, or Purified Protein Derivative (PPD) is derived from human strains of *M. tuberculosis* and consists of over 220 different antigenic components, of which most are low- and medium-weight proteins. Koch introduced the term 'tuberculin' in 1890 when he produced a filtrate from a culture of *M. tuberculosis* in an attempt to develop a TB vaccine. This filtrate became known as old tuberculin. Although recognised as a measure of hypersensitivity to TB proteins by von Pirquet in 1907, Koch's old tuberculin was abandoned because it lacked therapeutic benefit. In 1908, Mantoux described the intradermal skin test using old tuberculin—a test now known as the Mantoux test.

Seibert developed PPD in 1934 and a standardised preparation (PPD-S) was prepared by 1939. A variety of tuberculins produced from different strains using different methods now exist and are 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, however, are subject to significant cross-reactivity with other species of mycobacteria, including Bacille Calmette-Guerin (BCG)-bovis, and many environmental mycobacteria such as *M. avium* complex. (MAC). This cross-reactivity results in a significant reduction in both sensitivity and specificity. A positive response on skin testing, therefore, is a measure of past or current infection with one or more mycobacterial species.

In Australia, Commonwealth Serum Laboratories (CSL) produces tuberculin PPD-S (Human) in the following solution strengths:

- 100 IU (0.002 mg) per ml—1ml
- 100 IU (0.002 mg) per ml—10 ml
- 1000 IU (0.02 mg) per ml—1ml.

Tuberculin solution also contains a detergent, Tween 80, to minimise the adsorption of tuberculin proteins onto the walls of glass and plastic containers. This allows for prolonged storage and improves the reproducibility of the test.

Other tuberculins have been produced—including to *M. bovis*, *M. avium* and other environmental species such as *M. battey*—and can be used in some situations for differential testing.

2.2 The Mantoux Test

The tuberculin skin test (TST) is not a test for immunity to TB, but rather a measure of the degree of tuberculin hypersensitivity as measured by a cell-mediated immune response. The Mantoux test, the Heaf test and the tuberculin tine test—all variants of the tuberculin skin test—can deliver tuberculin PPD into the skin. In Australia, the Mantoux test is used virtually exclusively.

The Mantoux test is subject to variability in both injection and reading technique, but many of the inherent variations in the test's administration and interpretation 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. For this reason, it is preferable that only a relatively small number of individuals in an institution are responsible for performing and reading the test, to reduce reader variation.

2.2.1 Dose of Tuberculin

In Australia, the standard dose of tuberculin is 10 IU—that is, 0.1ml of a 100 IU per ml solution injected intra-dermally.

In many countries, the standard dose is 5 IU. Australia's former National Tuberculosis Advisory Council decided in the 1950s to adopt a higher dose of tuberculin (10 IU) in order to achieve increased specificity for the test, given the relatively high background incidence of environmental mycobacterial exposure in children and young people (especially to *M. avium* complex), particularly in the northern half of the country.

2.2.2 Procedure

The test is performed on an area of healthy skin, away from obvious blood vessels on the left forearm, at the junction of the upper and middle thirds. Wiping with acetone, ether or alcohol cleans the area, and the skin is allowed to dry before the test.

A tuberculin syringe with a 26-gauge, 13 mm long intra-dermal needle is used to inject 0.1 ml of tuberculin intra-dermally, with the bevel facing upwards so as to produce a 'bleb' or wheal of 5-8 mm diameter. The bleb should disappear within one hour. If the test produces no bleb, then the injection is too deep. Or, if some of the fluid escapes, then the test is not valid and should be immediately repeated at the same site on the other forearm.

2.2.3 Reading

The test is optimally read after 48-72 hours, although reliable results can be obtained up to five days after injection. Any reaction observed before 48 hours may not be due to tuberculin hypersensitivity and should be ignored. At the time of reading, the tester uses a small ruler to measure the transverse diameter (across the forearm) of any area of induration (not erythema) and records the result in millimetres.

2.2.4 Interpretation (in the Absence of BCG Vaccination)

Based on the sensitivity and specificity of the Mantoux test and the prevalence of TB infection in different sub-groups of the population, three cut-off diameters are recommended for defining a positive reaction: more than or equal to 5 mm; more than or equal to 10 mm; and more than or equal to 15 mm respectively (Table 1). For persons at highest risk of developing TB disease if they become infected with *M. tuberculosis* (for example, HIV-positive or otherwise immunosuppressed persons and close contacts of active smear-positive cases), a cut-off of more than or equal to 5 mm is recommended. For persons with an increased risk of recent infection (for example, recent immigrants and injecting drug users), a reaction of more than or equal to 10 mm should be considered positive. For all other, more than or equal to 15 mm is the recommended cut-off.

Table 1: Criteria for Tuberculin Positivity, by Risk Group (adapted from ATS/CDC, 2000)

Reaction ≥ 5 mm	**Reaction ≥ 10 mm**	**Reaction ≥ 15 mm**
HIV-positive persons	Recent immigrants from high TB-prevalent countries	Persons with a history of risk factors for TB
All recent contacts of active TB patients	Injecting drug users	History (including a scar) of BCG vaccination
Fibrotic changes on chest x-ray consistent with past TB	Residents and employees of correctional facilities, nursing homes, hospitals and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (including those on oral steroids of more than or equal to 15 mg per day of Prednisolone or equivalent for one month or more)	Mycobacteriology/microbiology laboratory personnel	
	Children younger than 4 years of age, and infants, children and adolescents exposed to adults at high risk	
	Persons with the following clinical conditions which place them at a higher risk: silicosis, diabetes, chronic renal failure, some haematological disorders (for example, leukaemias, lymphomas and other malignancies such as carcinoma of the lung, head or neck), a gastrectomy, a jejunoileal bypass, or weight loss of more than or equal to 10 per cent of ideal body weight	

Source: Adapted from American Thoracic Society and Centers for Disease Control & Prevention (2000).

2.2.5 BCG and the Tuberculin Skin Test

Previous vaccination with BCG frequently causes problems for the interpretation of the TST. The following points have an effect on the significance of a positive result:

- In ideal circumstances, with good-quality BCG and proper application, 90 per cent of BCG-vaccinated individuals will have a positive TST three months later.
- The mean size of skin test reactions in BCG-vaccinated children ranges from 3 mm to 19 mm (usually 12 mm), but the intensity of tuberculin hypersensitivity following BCG vaccination decreases over time.
- The persistence of tuberculin reactivity after BCG vaccination increases with the intensity of the local BCG reaction at the time of vaccination, and with the size of the residual BCG scar. As many as 25 per cent of vaccinated individuals, however, may fail to develop scars. Scar formation does not always correlate well with tuberculin reactivity. There is also a significant increase in the size of the tuberculin reaction with the increasing frequency of BCG vaccination and, consequently, with the greater number of BCG scars.
- Natural history studies estimate that this form of tuberculin hypersensitivity wanes at a rate of 10 per cent per year, unless repeated doses of BCG (or tuberculin) are administered on a regular basis (for example, each year). A positive TST result in adolescence or later cannot be assumed to be attributable to childhood BCG.
- A single BCG vaccination in early childhood (before 5 years of age) is likely to be followed by a negative TST response when testing is performed after 10 years or more. Any reaction of 10 mm or greater in this setting is significant, and should not necessarily be attributed to BCG.
- In persons inoculated at a later age, tuberculin sensitivity persists longer. A positive TST reaction need not be attributable to *M. tuberculosis* infection if the individual does not belong to a recognised high risk group and does not have known exposure.
- No reliable method has yet been developed to distinguish positive reactions due to previous BCG from those caused by natural mycobacterial infection, although BCG is unlikely to cause reactions of 20 mm or more of induration.
- The persistence of tuberculin hypersensitivity for seven to 10 years after BCG vaccination may be due to a booster effect (see below) of natural infection with *M. tuberculosis* or a non-tuberculous mycobacterial infection.

Repeated TST on uninfected/unvaccinated individuals does not sensitise them to tuberculin. The larger the reaction, the greater is the probability that the responsible organism is *M. tuberculosis*.

In summary, for the individual with a past history of BCG vaccination, the probability that a positive TST results from exposure to *M. tuberculosis* increases when:

- The size of the reaction increases.
- The individual is a contact of a person with active TB disease, especially if that person is known to have infected others.
- There is a family history of TB.
- The individual's country of origin is known to have a high incidence of TB.
- The length of time between BCG vaccination and TST increases.
- BCG vaccination was given at an early age.
- There is a history of occupational exposure or an increased risk of occupational exposure.

2.2.6 Two-Step Testing (Booster Phenomenon)

Two-step tuberculin testing implies repeating the TST 1 – 4 weeks after an initially negative TST. The purpose of two-step testing is to determine whether the initial TST has resulted in the recall of a weak or waning immune response to tuberculin, often referred to as the 'booster phenomenon'. Boosted responses are important in persons such as health care workers who undergo serial TST, because repeat testing may result in an increase in the size of the reactive induration, that may be incorrectly interpreted as a

conversion and lead to unnecessary preventive therapy.

The booster phenomenon can occur at any age, but is more likely to occur in persons over 50 years old. It results from previous mycobacterial sensitisation (often many years earlier) via previous exposure/infection, BCG immunisation or exposure to non-tuberculous environmental mycobacteria such as *M. avium*, of which the immunological memory has waned over time. Boosting can occur as early as one week after an initial TST and can persist for a year or more.

An increase of 6–10 mm in the diameter of induration from a second TST may represent, therefore, a boosted response rather than a true conversion following recent exposure, provided that the second TST is undertaken no longer than two to three weeks after the first TST. Beyond this time, the possibility that the increase in the reaction is the result of a true conversion increases significantly, to a maximum at about six to eight weeks. Whether a second TST reaction should be interpreted as either a false positive or a false negative response (that is, the booster phenomenon or possible recent infection) depends on that individual's clinical circumstances.

2.2.7 False Negative Tuberculin Skin Test

A false negative TST is a TST that is negative in the presence of TB infection. It can be obtained when:

- Out-of-date tuberculin is used.
- Tuberculin leaks at the injection site.
- Testing is undertaken too early in cases of primary exposure, before hypersensitivity has developed. (A hypersensitivity reaction generally takes six to eight weeks to develop.)
- The injection is too deep.
- The test reading is undertaken too early (before 48 hours) or too late (after one week).
- The person has an inter current viral infection (such as measles) or has had a recent live viral immunisation.
- The person is undergoing corticosteroid therapy (especially if long term) or immunosuppressive therapy.
- The person is suffering from malnutrition, perhaps from a period in a refugee or prison camp, or from significant cachexia.
- The person is elderly.
- The person has a medical condition that may result in partial immunosuppression, such as diabetes, sarcoidosis, advanced alcoholism, renal failure, massive trauma or burns.
- The person is an injecting drug user.
- The person has any malignancies, especially lymphoma.
- The person has HIV/ AIDS.
- The person is seriously ill, including when they have advanced or miliary TB.

2.2.8 False Positive Tuberculin Skin Test

A false positive TST can occur as a result of:

- Recent BCG vaccination
- A ruptured small venule at the time of injection
- Faulty test interpretation, such as the measurement of erythema rather than of induration.

2.2.9 Adverse Reactions

Adverse reactions to TST are rare. Vaso-vagal reactions can occur, as with any injection. An immediate wheal and flare reaction with a localised skin rash can occur, but without evidence of induration at 48–72 hours. Anaphylaxis is very rare and not associated with positive reactions.

In strong positive reactions, the possible side effects include blistering (even ulceration at the site of injection) and, on occasions, lymphangitis above the reaction. Epi-trochlear or axillary lymphadenitis rarely occurs with strongly positive reactions.

At the site of injection, residual erythematous lesions that persist for extended periods (months to years) are not uncommon following strongly positive reactions. Recall responses (that is, a spontaneous recurrence of an indurated and/or erythematous reaction) are reported to have occurred a year or more after injection. As yet, there is no reasonable explanation of this phenomenon.

2.3 Who Needs a Tuberculin Skin Test?

Tuberculin skin testing should be performed to identify any person who may be at an increased risk for TB and who may benefit from treatment of latent TB infection. It is desirable, therefore, 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 may place them at increased risk of exposure (such as health care workers). Likewise, TST should always be considered where there is a clinical likelihood of active TB disease.

In summary, consider TST in the following situations:

- Recent contacts of persons known to have, or 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 TB). If the initial test is negative, then consider retesting at eight weeks (see Chapter 16, 'Contact Tracing').
- Persons with HIV infection
- Injecting drug users
- Persons with abnormal chest X-rays suggestive of previous TB
- Persons with other medical conditions that increase the risk of TB (silicosis, diabetes mellitus, prolonged corticosteroid therapy, immunosuppressive therapy, some haematological and reticuloendothelial diseases, end-stage renal disease and clinical situations associated with rapid weight loss)
- Groups at high risk of recent infection with *M. tuberculosis* (immigrants from Asia, Africa, Central America, Oceania, Eastern Europe and the former Soviet Union; medically underserved populations, and personnel and long term residents in some hospitals, nursing homes, mental institutions and correctional facilities)
- Health care workers at risk of infection with *M. tuberculosis* (see Chapter 7, 'Preventing TB Infection and Disease among Health Care Workers').

2.4 QuantiFERON-TB Assay

The Commonwealth Scientific and Industrial Research Organisation (CSIRO) and Commonwealth Serum Laboratories Biosciences recently jointly developed a new blood test that is able to measure quantitatively the production of the cytokine Interferon-γ by lymphocytes sensitised to mycobacterial proteins using an ELISA technique. This assay, QuantiFERON-TB, now marketed by Cellestis Limited, is the only available assay of its type in the world. It is being evaluated in a number of countries (by the Centers for Disease Control and Prevention in the United States in large multi-centre trials) as a replacement for the TST and already has FDA approval for this purpose.

QuantiFERON-TB has the potential to overcome several difficulties associated with the TST, by involving only one visit for a blood sample, having no injection technique problems, avoiding subjective interpretation of results, and having significant cost benefits. The assay is available from only one or two approved pathology providers in Victoria at this time.

The assay does, however, suffer from a reduction in specificity and sensitivity inherent with the use of tuberculin (PPD-S) as a test antigen. The planned introduction of specific antigens for *M. tuberculosis*, such as ESAT-6 or CFP-10 should result in improved sensitivity and specificity for *M. tuberculosis* and *M.bovis*, without cross-reacting with BCG-bovis or MAC. Further studies are under way both in Australia and overseas, with a view to confirming these hypotheses. Presently, the assay is rebateable by Medicare only if it is performed on those persons known to be, or suspected as being, HIV positive.

2.5 Information for Service Providers

How does a service provider learn how to do a Mantoux skin test, interpret the results and institute an appropriate clinical response? The TB Program, Department of Human Services, offers a training program for service providers in performing and reading Mantoux tests and also in BCG vaccination. Contact the TB Program Nurse Manager on (03) 9637 4110 or email lynne.brown@dhs.vic.gov.au.

Mantoux tests can be performed at local public hospitals (where the infection control practitioner can advise if the service is available), by pathology providers (remembering that TST for screening purposes without a specific clinical indication does not attract a Medicare benefit) and by local general practitioners who have been trained in the technique. If in any doubt, contact the TB Program Nurse Manager on (03) 9637 4110 or email lynne.brown@dhs.vic.gov.au.

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3. Laboratory Diagnostic Services for TB and Other Mycobacterial Diseases

3.1 Introduction

TB control programs depend on laboratory services for the reliable and timely confirmation of the presence of *M. tuberculosis* (MTB) or other non-tuberculous mycobacteria in clinical specimens. The minimum necessary laboratory functions available to the State should include:

- Microscopy using acid-fast (Ziehl-Nielsen) stain
- Culture on appropriate TB media
- Definitive speciation of isolates
- Anti-tuberculous drug susceptibility testing.

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

- 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
- Assessment and provision of rapid diagnostic tests such as nucleic acid testing on fresh or fixed tissue
- Provision of training and a consultation/advisory service to other laboratories and health professionals
- Ongoing research and development in mycobacteriology
- Provision of veterinary and environmental mycobacteriology services 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 carrying out mycobacterial tests has been proposed for adoption in Australia.

3.2.1 Level 1 Laboratories

The majority of general bacteriology laboratories, as found in small hospitals and private pathology laboratories, are level 1 laboratories. They should make direct acid-fast microscopy available at short notice, but should not attempt culture for mycobacteria. They refer specimens to a higher level facility for both confirmatory microscopy and culture. These smaller laboratories should seek advice from the State Mycobacterium Reference Laboratory on less common requests, such as optimum specimen collection for the diagnosis of non-tuberculous mycobacterial infections.

3.2.2 Level 2 Laboratories

Level 2 laboratories are larger laboratories (both public and private) that would receive regular requests for the diagnosis of mycobacterial infections, especially TB and *M. avium* complex infections. Such laboratories perform both acid-fast microscopy and mycobacterial culture. They generally do not perform definitive species identification, although this could change with new technology such as radiometric culture and DNA probes.

All new isolates of *M. tuberculosis*, as well as any potentially pathogenic atypical mycobacteria, must be forwarded to a level 3 laboratory for further testing. If a level 2 laboratory receives specimens for mycobacterial culture for pathogens that require special culture media or conditions, then it may be more cost-effective for the laboratory to refer these specimens directly to a level 3 laboratory.

3.2.3 Level 3 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. These laboratories also should provide support to lower level laboratories in the form of advice, training and the provision of reference methods and mycobacterial strains. They should collate statistics (particularly those dealing with new diagnoses of TB and antibiotic susceptibility patterns) and provide them to public health authorities. They also should be involved in the development or evaluation of new tests such as those involving molecular procedures for rapid diagnosis, speciation, susceptibility testing and epidemiological sub-typing of isolates. Environmental mycobacterial outbreak investigations are best coordinated by the State Mycobacterium Reference Laboratory.

Level 3 laboratories should communicate with other interstate Mycobacterium Reference Laboratories to provide highly specialised but infrequently required tests such as mycolic acid analysis by HPLC (high performance lipid chromatography), and also to exchange epidemiological information and mycobacterial strains as necessary. The Victorian Mycobacterium Reference Laboratory at the Victorian Infectious Disease Reference Laboratory is the only level 3 facility in Victoria.

3.3 Quality Assurance

All clinical laboratories performing diagnostic mycobacteriology at any level must carry current National Association of Testing Authorities / Royal College of Pathologists Australasia (NATA/RCPA) accreditation for these procedures. This accreditation includes participation in proficiency testing programs appropriate to the level of service provided by the laboratory.

3.4 Standards

The Mycobacteria Special Interest Group of the Australian Society for Microbiology has aimed to standardise methods used by 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 cooperative 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.

3.4.1 Microscopy

Laboratories should routinely perform microscopy on all specimens submitted for acid-fast bacilli (AFB) examination except blood and urine, using Ziehl-Nielsen and/or fluorochrome staining. They should attempt to quantify the number of AFB present in any positive smear.

3.4.2 Culture

Laboratories should perform culture using a validated commercial system, egg-based solid media or a combination of these. Certain species such as *M. bovis*, *M. haemophilum*, *M. marinum* and *M. ulcerans* have special requirements in media and/or temperature of incubation. To ensure appropriate cultures are performed, clinicians and the laboratory need to communicate. All cultures should be read at weekly intervals for at least six weeks. Direct culture remains the most sensitive and preferred isolation technique.

3.4.3 Identification

Level 3 facilities should have the expertise to identify all human pathogens. They may identify *M. tuberculosis* and related species by traditional criteria, such as niacin production, nitrate reduction, cord formation, lack of growth at room temperature and drug susceptibility. Commercial DNA probes are now an acceptable alternative means of identification. These provide rapid results but will not provide speciation within the *M. tuberculosis* complex.

Laboratories should identify all isolates of atypical mycobacteria that are likely to be pathogens—for example, repeat isolates from sputum and isolates from sterile sites, tissues and wounds. Adequate clinical data are essential for determining the pathogenic role of such isolates. Authoritative texts

and recently published studies provide adequate reference sources for procedures and identification strategies.

3.4.4 Susceptibility Testing

Only level 3 facilities should perform susceptibility testing. All *M. tuberculosis* complex initial isolates, as well as repeat isolates from relapse cases or 'treatment failures', should be tested for susceptibility to at least isoniazid, ethambutol, rifampicin and pyrazinamide. Susceptibility to additional drugs is tested when resistance to first-line agents is found.

The value of susceptibility tests on slow growing atypical mycobacteria remains controversial. Most Mycobacterium Reference Laboratories do not routinely perform drug susceptibility testing of slow growing species such as *M. avium* complex (MAC) routinely, because clinical correlates between in-vitro test results and clinical response 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 Mycobacterium Reference Laboratory. Some species (for example, *M. kansasii*) have such uniform susceptibility patterns that little can be gained from routinely testing individual isolates except in the case of treatment failure. Rapidly growing species such as *M. fortuitum* should be tested by disc diffusion, agar dilution or E-test against a range of drugs, including tetracyclines, amino-glycosides and sulphonamides. Laboratories may perform occasional surveys of drug susceptibility on stored isolates of some atypical mycobacteria, such as *M. marinum*, as an aid to clinical management.

3.5 Recent Technological Developments

The development of commercial semi-automated liquid medium systems (for example, Bactec™ or MGIT™) has allowed more rapid isolation of mycobacteria, including *M. tuberculosis*. Data accumulated from numerous centres in the past decade confirmed the improved speed, reliability, sensitivity and reproducibility of these methods. An advantage of the systems is that they can provide a safe, efficient method for recovering mycobacteria from the blood of patients infected with HIV.

New nucleic acid amplification (NAA) procedures, such as polymerase chain reaction (PCR), promise to revolutionise diagnostic mycobacteriology, but NAA technology is not yet perfected and the sensitivity is still not as high as that of modern culture methods. 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 by 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.

Other PCR-based assays suitable for use on fresh or fixed tissue specimens are under development and validation. The MRL should be contacted for advice on test availability and specimen collection if there is a difficult diagnostic situation in which NAA testing will be required. Molecular sub-typing of strains of *M. tuberculosis* by restriction fragment length polymorphism (RFLP) analysis is an important tool in epidemiological studies of TB. 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. The MRL also provides mycobacterial DNA sequencing techniques to help identify unusual organisms.

Acknowledgments

This chapter draws on documents prepared by Mr David Dawson of the Queensland Mycobacterium Reference Laboratory and Professor Lyn Gilbert of the New South Wales Mycobacterium Reference Laboratory for policy development for other Australian State and Commonwealth Health Departments. These documents reflect the views of the Mycobacterium Special Interest Group of the Australian Society for Microbiology.

4. Treatment of TB

4.1 Treatment of Active TB Disease

All tuberculosis chemotherapy regimens used in Victoria should be in accordance with the current National Health and Medical Research Council guidelines. The current edition of 'Antibiotic Guidelines' provides basic guidance. For more specific detail, refer to *Tuberculosis in Australia and New Zealand into the 1990s*.

4.2 Treatment Regimens

A variety of combination treatment regimens can be tailored to specific patient requirements. The particular regimen chosen must ensure medication is taken regularly (preferably supervised by others), in an appropriate bactericidal combination, with adequate doses and of sufficient duration to prevent the emergence of resistant strains, while effectively sterilising the infection.

At the commencement of treatment, all persons should initially be considered to have an isoniazid-resistant organism until sensitivity patterns are known. Then, the treatment regimen can be adjusted accordingly. Treatment should include the four primary drugs—isoniazid (H) + rifampicin (R) + pyrazinamide (Z) + ethambutol (E) (see box below)—taken together for the first two months, with a further continuation phase of H+R for at least another four months (that is, 2HRZE4HR).

Medications should be taken on a daily basis for at least the first month, with either daily or intermittent treatment thereafter until completion. If an intermittent regimen (twice or three times weekly) is used, then medication doses MUST be fully supervised. Treatment periods of less than six months duration have a higher failure rate, so should be avoided. Note that ethambutol is a bacteriostatic 'companion' drug and cannot be used as a replacement for one of the bactericidal agents when there is drug resistance or patient intolerance.

In Victoria, all primary TB drugs are provided FREE of CHARGE to notified patients. A public health nurse is allocated to each case to undertake appropriate contact surveys, supervise treatment to completion, and act as a liaison person for patients and their families. Treating physicians are encouraged to make full use of the support services available to patients through the TB Program, and to liaise directly with either the Nurse Manager of the TB Program or the TB nurse allocated to the case.

Treating physicians are requested to ensure all patients and/or their carers are supplied with written information, in an appropriate language where possible, about the treatment of TB, drug side-effects and follow-up plans. Supplies of printed materials may be obtained from the TB Program.

The Current Standard Treatment Regimen for All Patients

Isoniazid (H):	300 mg daily, in a single dose, morning or evening, preferably before a meal, for six months
Rifampicin (R):	Weight > 50 kg—600 mg daily, taken $^1/_2$–$^3/_4$ hour before food, preferably in the morning, for six months Weight < 50 kg—450 mg daily, taken $^1/_2$–$^3/_4$ hour before food, preferably in the morning, for six months
Pyrazinamide (Z):	25 mg per kg of body weight, to a maximum of 2000 mg daily, in a single dose, with or after food, for the first two months
Ethambutol (E):	15–25 mg per kg of body weight daily, in a single dose, with or after food, for the first two months (*Note:* if serum creatinine is greater than 110mmol/L, then a lower dose of 15 mg per kg should be used. Visual acuity should be serially assessed while the patient is taking Ethambutol, especially if there is evidence of impaired renal function.)

These notes are provided only as a guide. Any medical practitioner proposing to treat cases of active TB should be aware of the risks and nature of the side effects associated with each of the above compounds, and with the precautions required for safe management of each case.

The management of drug-resistant TB (especially to rifampicin and isonaizid—that is, multidrug-resistant TB, or MDR-TB) is outside the scope of these guidelines, and should be undertaken by only an appropriately experienced consultant, preferably at a specialist infectious diseases unit. The 'second-line' drugs required for the treatment of drug resistant cases (for example, streptomycin, fluoro-quinolones, prothionamide, cycloserine, amikacin, capreomycin, PAS, rifabutin, clarithromycin, clofazimine) have significant toxicity, are of limited effectiveness, are often difficult to obtain, and have considerable cost. Treatment regimens for drug-resistant TB are generally of 18–24 months duration, although shorter periods of treatment may be appropriate in some cases when the regimen can include surgical resection. Side effects are generally universal and usually the determining factor for completion.

Table 2: TB Drug Side Effects and Drug Interactions

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

4.3 General Principles

- **NEVER** use mono therapy, except when treating latent TB infection with isoniazid (H).
- **NEVER** add only one drug to a failing regimen; always use at least two additional bactericidal drugs wherever possible.
- **NEVER** use short course (six month) treatment regimens (continuous and intermittent) if:

  a) pyrazinamide (Z), in proper dose, is not part of the initial regimen

  b) and/or there is evidence of drug resistance

  c) there is failure to convert to negative smear/culture after two months

  d) there is evidence of immunosuppression.

  In these clinical situations, treatment duration MUST be extended for at least NINE months, even up to 12-18 months using appropriate regimens for the individual case (specialist advice desirable).
- Use fully supervised chemotherapy whenever possible. This is an essential requirement for patients being treated with intermittent regimens. Support and guidance can be obtained through the TB Program. This requirement for supervision includes those treatment regimens for latent TB infection that use two or more drugs.
- Never assume compliance with drug therapy even with the fullest assurance that all is going well. Check for the presence of drug metabolites in urine, check sputum regularly to ensure conversion to negative acid-fast bacilli smear/culture and encourage family members to be involved in supervising and ensuring regular medication use.
- Commence a treatment regimen cautiously. There is NO rush to start a person on full treatment in the majority of cases. Remember that *M. tuberculosis* has a slow 'doubling time' of approximately 48 hours and that treatment needs to be given in 'pulses' to achieve adequate blood levels. Introduce drugs progressively, therefore, especially in the elderly and in those with hepatic and renal impairment. A suggested plan is to start with isoniazid (H) and ethambutol (E), then to introduce rifampicin (R) seven to 10 days later (provided that liver function is holding) and, lastly, to introduce pyrazinamide (Z) a week or so later (again, only if liver function is satisfactory). Reduced doses of H, R and Z may be necessary initially (especially in the elderly), with increments in dose as tolerance improves. The elderly are particularly intolerant of pyrazinamide.
- Consider the possibility that patients with acute or chronic hepatic and renal disease may require significant modification of their treatment regimens and drug doses, depending on their individual clinical situation, sensitivity patterns and drug tolerance. The presence of hepatic or renal disease, however, does not necessarily preclude the use of a standard treatment regimen.
- Provide all patients and their carers with (a) written information about the effects and side-effects of their drugs, together with (b) advice on being alert to symptoms and (c) contact details for the treating physician/hospital clinic and the public health nurse allocated to the case. These written instructions are to be in the appropriate language for the patient. The public health nurse will provide each patient with a treatment pack, which includes a 'Dosette' box.
- Remember, while younger patients generally tolerate treatment well and usually can commence all medications at once, there are exceptions. Early review of patient response is desirable, especially in clinical situations where there is evidence of co-infection (HIV, hepatitis B, hepatitis C), complicating systemic or other organ disease (renal, hepatic) or a need for other treatment regimens such as anti-retroviral medications (see Chapter 11, 'HIV Infection and TB').
- Conduct regular monthly sputum examinations of all sputum smear-positive patients to ensure conversion is maintained.
- Note that patient follow-up is not normally indicated after two years from completion of treatment where there has been adequate resolution of disease using at least six months of preferably fully supervised therapy.

- Review patients with HIV/AIDS indefinitely. Persons with immunosuppression who have fully sensitive organisms generally require only a standard treatment regimen of six months, but a longer duration of treatment with an appropriate regimen is required if there is any evidence of drug resistance.
- Encourage patients, after their discharge from follow-up, to make contact with medical care if any symptoms recur. Give them sufficient clinical data, including copies of chest x-rays, for later comparison if required.
- Treat drug-resistant infections and persistent or chronic infections only in conjunction with recognised consultants in TB management, preferably at a specialised infectious diseases unit. In some instances, surgical resection may be indicated.
- Note that corticosteroids are rarely indicated in the management of acute TB infection, except when treating tuberculous meningitis or TB pericarditis. Evidence of beneficial effect is much less in other forms of extra-pulmonary TB and there is no current indication for corticosteroids in the treatment of pulmonary TB.

4.4 Non-Tuberculous or Opportunistic Mycobacterial Infections

Non-tuberculous or opportunistic mycobacterial infections are mentioned because their frequency of isolation is increasing, especially in the clinical context of immunosuppression. The majority of these organisms are generally resistant to routine agents, and the management of these infections is usually difficult and prolonged. Not infrequently, conventional agents cannot control the infection, and other treatment modalities (such as immunotherapy, surgery or the use of cytokine supplements) need to be considered. Management should be undertaken only in specialist infectious diseases units. These mycobacterial infections, other than for leprosy (*M. leprae*), are not notifiable in Victoria.

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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 the development of secondary drug resistance. Studies have shown that compliance with TB treatment cannot be predicted; compliance is not related to socio-economic status, the severity of disease, the presence of drug side effects or the patient's educational level or understanding of disease (Sbarboro, 1990).

5.2 Directly Observed Therapy (Short Course) in TB Control

The World Health Organisation is campaigning strongly for all national TB programs to implement the directly observed therapy (short course) (DOTS) approach to achieve global TB control. In 1998, DOTS programs were accessible to 43 per cent of the world's population (World Health Organisation, 2001).

DOTS programs include strategies to improve TB detection and treatment outcomes, including:

- Directly observed administration of drugs
- Short course (six month) treatment
- A reliable, affordable supply of drugs
- Case detection (laboratory confirmation, particularly smear-positive pulmonary TB)
- Reliable surveillance, including recording and reporting
- Government commitment to TB control.

In its most simplistic form, DOTS relates to the supervised swallowing of medication. The World Health Organisation, the US Centers for Disease Control and Prevention, and the Australian National Health and Medical Research Council advocate it as the preferred method of TB treatment. In Australia, three of the eight States and Territories' TB programs have implemented DOTS methods, covering 37 per cent of the Australian population.

DOTS has proven to be superior to unobserved, supervised therapy and has been shown to reduce the rates of relapse and secondary drug resistance (Chaulk et al., 1995; Weis et al., 1994). There are limitations, however, in implementing a universal DOTS program within a given community. Directly observed therapy (DOT) can be resource intensive and may not be accepted by patients who find it difficult to cooperate with clinic attendances or home visits for the supervised administration of medication. This is particularly the case in developed countries where many patients are in full time employment or study. Strategies to supervise pill taking need to be creative and flexible, and require total commitment from both the patient and the observer.

5.3 Supervision of treatment in Victoria

In Victoria, compliance with treatment is monitored by treating physicians and the TB Program public health nurses. Successful completion of therapy is evidenced by low rates of relapse (less than 2 per cent per year). 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, questioning about pill taking and, possibly, random urine tests. The TB Program nurses monitor patients during home visits, telephone calls and clinic attendances, but medication is totally self-administered.

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

- Issuing a 'compliance pack' at initial notification. This pack includes a medication-dispensing box ('dosette'), language-specific information about medications and drug side effects, a pill recording chart and contact information details for the public health nurse. The nurse closely monitors the patient's comprehension and ability to use the 'dosette' box during the initial phase of treatment.
- Encouraging family support and enlisting a relative or significant other to supervise pill taking
- Making weekly visits to fill the 'dosette' box
- Ensuring adequate drug supplies by arranging scripts and/or delivering medications.

5.3.1 DOT in Victoria

Adherence to therapy should be assessed on an ongoing basis. Occasionally, the treating physician and/or the TB Program nurse will consider a patient at risk of non-compliance. In this event a case conference should be convened and attended by the patient, treating physician and the public health nurse. They should negotiate a DOT plan and select the most appropriate intermittent therapy regimen. In most instances, medications are given three times weekly in Victoria; however, in some States and Territories, twice-weekly therapy is becoming more frequently used. It is uncommon for DOT to be administered daily, particularly after the initial, sterilising phase of treatment.

The TB Program nurse may supervise pill taking, but in some circumstances, other health care providers or lay personnel will supervise medications (with TB Program support). The Royal District Nursing Service, local community health care or general practitioner clinics, campus nurses or personal care attendants may be approached to assist with supervision of treatment. The most important consideration is that both the patient and supervisor commit to the arrangements; a missed thrice- or twice-weekly dose has a greater impact on treatment outcome than has a missed 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. The use of enablers, such as help with transport to clinic appointments and incentives such as food vouchers, may encourage patient compliance.

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6. Hospital Care of TB

6.1 Introduction

Tuberculosis is transmitted in airborne particles, or droplet nuclei, that persons with pulmonary or laryngeal TB generate when they sneeze, cough, speak or sing. Normal air currents can keep infectious particles airborne for prolonged periods and spread them throughout a room or building. For this reason, a patient in hospital with active pulmonary TB represents a potential infectious hazard to other patients, carers and visitors. Tuberculous involvement of other organs (for example, renal, hepatic, gastrointestinal or meningeal TB) does not pose a significant risk of transmission unless associated with aerosolisation of infected material. This chapter focuses on methods of reducing the risk of hospital cross-infection, including patient isolation, the engineering requirements of the isolation room, and personal respiratory protection.

6.2 Identification of Patients with Confirmed or Suspected Active TB

Consider TB and make a decision about isolation for any patient who has:

- A cough that persists for three weeks
- Other signs or symptoms compatible with active TB—for example, bloody sputum and constitutional symptoms, including weight loss, fever and night sweats
- Chest x-ray changes consistent with pulmonary TB.

The techniques used to establish the diagnosis of TB are discussed elsewhere.

6.3 Guidelines for the Management of Hospitalised Patients with Confirmed or Suspected Active TB

6.3.1 Initiation of Patient Isolation

Many patients with TB can be satisfactorily managed at home. If admission to hospital is required—as a result of ill health from the TB or other co-morbid conditions, for social reasons, to ensure drug compliance, or for investigations to establish the diagnosis of TB—then a decision must be made about patient isolation.

- Place any patient with confirmed or suspected pulmonary or laryngeal TB in a TB isolation room that has recommended ventilation characteristics (see section 6.3.3). Patients requiring inpatient care in hospitals without such a facility should be transferred to a hospital where one exists. Isolation may sometimes be required for patients with non-pulmonary TB who require aerosol-generating procedures such as wound irrigation.
- Evaluate paediatric patients with confirmed or suspected active TB for potential infectiousness according to the same criteria as applied to adults (that is, on the basis of symptoms, sputum acid-fast bacilli (AFB) smears, radiological findings and other criteria).
- Treat patients with confirmed or suspected active TB in intensive care units the same as patients in non-critical care settings. Place them in TB isolation and have their respiratory secretions cultured and examined for AFB. For patients who are intubated and mechanically ventilated, place a suitable particulate filter in the exhalation side of the respirator circuit. For further advice on infection control relating to respiratory units, see the document *Infection Control Guidelines for Anaesthesia*, available from the Secretary, Victorian Advisory Committee on Infection Control (VACIC) Department of Human Services, on (03) 9637 4133.

- In general, nurse one patient with confirmed or suspected TB per room. Only nurse two patients in the same room if both patients have culture-confirmed TB with drug susceptibility patterns known to be identical, and if both patients are HIV negative.

6.3.2 General Isolation Practices for Patients with Confirmed or Suspected TB

- Educate isolated patients with confirmed or suspected TB and their visitors about the mechanisms of TB transmission. The patient should learn to cover their mouth and nose when coughing or sneezing to minimise the droplet spread of mycobacteria in expelled air.
- Ensure patients placed in isolation remain in their isolation room with the door closed. When patients need to be transported outside the isolation room, they should wear surgical masks to cover their mouths and noses during transport. Where possible, schedule investigative procedures for these patients when they can be performed rapidly and when patients are not held in crowded waiting areas for long periods.
- Keep the number of health care workers or visitors entering an isolation room to an absolute minimum. All persons entering an isolation room should wear a personal respiratory protection device (see Section 6.3.4).
- Although items contaminated with respiratory secretions are not usually associated with the transmission of TB, handle and transport these items in a manner that reduces the risk of transmitting micro-organisms to other patients, health care workers and visitors, and decreases hospital environmental contamination with TB. Transport sputum specimens collected from TB patients to the laboratory in clearly marked biohazard plastic bags.
- TB patients do not require separate crockery and bed linen.

6.3.3 Characteristics of the TB Isolation Room

Isolation rooms for patients with TB should be class N—that is, negative pressure type. The Standing Committee on Infection Control, Department of Human Services, defined the recommended elements of such a facility in the April 2000 publication, *Guidelines for the Classification and Design of Isolation Rooms in Health Care Facilities*.

- Optimal ventilation systems should be designed and constructed to maintain airflow from clean areas to less clean areas. TB isolation rooms should be single-patient rooms that are maintained under negative pressure. Doors to these rooms should be kept closed so the negative pressure can be regularly maintained. Qualified ventilation engineers should check the negative pressure in the rooms at regular intervals. The use of an anteroom leading into the isolation room may minimise the potential dissemination of AFB into nearby corridors.
- For TB isolation and treatment rooms, the recommended ventilation is a minimum of 12 air changes per hour. The effectiveness of this level of airflow in reducing the concentration of AFB in such rooms, however, has not been directly or adequately evaluated.
- Air from TB isolation and treatment rooms should be exhausted to the outside atmosphere and not recirculated into the hospital's general ventilation. Exhaust airflow dynamics need to be examined to ensure potentially contaminated air from TB isolation rooms is not externally exhausted in a manner that may result in its re-entry into the inflow side of the hospital's ventilation system. For a more detailed description of the engineering requirements for TB isolation rooms, see *Guidelines for the Classification and Design of Isolation Rooms in Health Care Facilities*, available from the Department of Human Services, on (03) 9637 4133 or on the Internet at http://www.dhs.vic.gov.au/phd/9906058a/index.htm.

- All acute care inpatient facilities should have at least one appropriately ventilated TB isolation room; in some cases, depending on the institution's patient mix, a number of rooms may be necessary. Refer to the abovementioned guidelines for a detailed account of how to determine the appropriate number of isolation rooms.

6.3.4 Personal Respiratory Protection Devices

Detailed information concerning the transmission of TB is incomplete in the sense that we have not conclusively defined issues such as the smallest infectious dose of TB and the level of exposure to TB at which transmission occurs. In settings where the likely exposure to health care workers of airborne droplet TB nuclei is high, the use of personal respiratory protective devices may be of benefit. For a detailed description of such devices, see 'Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities' (Centers for Disease Control, 1994).

A recent review of the use of masks when caring for TB suggested 'masks should be seen as an adjunct to the more important measures of prompt identification, isolation, treatment, and environmental controls' (Curran and Ahmed, 2000). There are two main types of personal respiratory protection device: surgical-style masks and high efficiency particulate air (HEPA) respirators.

Surgical-Style Masks

Surgical masks were originally designed to prevent contaminated droplets from theatre staff falling into the operative site, not to provide a tight face seal. In their original form, they probably give little protection to the wearer against airborne droplet infection. Recent improvements in design have made such duckbill-style masks more effective filters and improved the face seal. Masks appropriate to this use incorporate P3 (Australian Standard) filter material, which has 99.5 per cent efficiency against particles in the 0.3-0.5 micron range, and are known as 'sub-micron masks'. The Australian standard also prescribes certain standards for face seal effectiveness. The weak point of such masks is the closeness of fit to the face; wearers should take care to ensure optimum adjustment when wearing such a mask. Sub-micron masks are referred to by a variety of names, including 'particulate filter' and 'respirator' mask.

Masks should be worn by:

- Patients suspected of having TB when not in TB isolation rooms
- All persons entering the room in which patients with known or suspected active TB are isolated
- Health care workers caring for the patient where cough-inducing or aerosol-generating procedures are used.

Particulate Respirators

Particulate respirators are designed to filter the air before the person wearing the respirator inhales that air. The Centers for Disease Control and Prevention recommend that health care workers use HEPA filter respirators to protect against patient-acquired TB infection. The Centers for Disease Control (1994) recommends that these respirators meet the following performance criteria:

- The ability to filter particles 1 micron in size in the 'unloaded' state, with the filter efficiency of 95 per cent given flow rates of up to 50 litres per minute
- The ability to obtain a face seal leak of 10 per cent
- The ability to fit different facial sizes and characteristics of health care workers.

Particulate respirators may be more effective than surgical masks in filtering mycobacterial aerosols, but whether this difference is sufficient to abandon the use of the surgical-style masks by health care workers in favour of particulate respirators remains controversial. A study (Chen, Vesley and Brosseau, 1994) that compared the filtration efficiency against mycobacterial aerosols of submicron surgical masks, dust-mist respirators and HEPA filter respirators found little difference among these three devices, with filtration efficiencies ranging from 97.2 per cent for surgical masks to 99.99 per cent for HEPA filters. One study (Jernigan et al., 1994) suggests that the protective efficiency and cost-effectiveness of particulate respirators is likely to be low compared

with the use of sub-micron surgical masks and strict TB isolation measures.

Recommendations to use HEPA filter respirators routinely therefore remain controversial. No comparative epidemiologic data are available to support the use of HEPA filtration respirators over appropriately fitted submicron surgical masks (Adal et al., 1994).

The potentially higher level of protection offered by personal use particulate respirators should be considered, particularly if health care workers are repeatedly exposed to the following situations where the risk of TB transmission may be especially high:

- Performing bronchoscopy of patients with active TB
- Undertaking an autopsy on patients with active TB
- Caring for mechanically ventilated patients with active TB where an exhalation filter is not fitted
- Attending patients with active multidrug-resistant TB (MDR-TB).

6.3.5 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, homogenising or lyophilising of TB-infected tissue. Such procedures should be performed on patients with confirmed or suspected TB, or on TB-infected tissue, only in an appropriate isolation area.

Health care workers exposed to potentially infectious aerosolised material should wear a suitable personal respiratory protection device 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 area until coughing has subsided. During this period, they should be instructed to cover their mouths and noses with disposable tissues when coughing. Where a cough-inducing or aerosol-generating procedure takes place, sufficient time should be allowed after the patient's departure from the room to allow for the efficient removal of airborne contaminants. The time required depends on the number of air changes per hour.

6.3.6 Staff and Other Patients as Contacts

Health care workers in occasional brief contact with pulmonary TB patients are at low risk of infection, but need to be included in regular educational sessions about TB so they are aware of the possible TB symptoms that they should report. Staff sometimes have more prolonged contact, which may include hours of nursing care or chest physiotherapy, for example. Such staff, along with any patients sharing a room with an infectious TB patient for long enough to be a 'household contact', may need contact tracing follow-up (see Chapter 16, 'Contact Tracing').

6.4 Cessation of TB Isolation

6.4.1 Discontinuation of TB Isolation

TB isolation can be discontinued in the following situations:

- The diagnosis of TB has been ruled out.
- The patient is no longer regarded as infectious—that is, the patient has had a minimum of two weeks of effective therapy, understands and tolerates the medications, is improving clinically and has three consecutive AFB negative sputum smears on different days.

Some patients continue to discharge non-viable organisms in sputum for some weeks after commencement of effective therapy. The fact that they are non-viable, however, can be established with certainty only when cultures become available six to eight weeks later. It is hard to judge when to release such patients from isolation; this decision should be made in close consultation with a physician experienced in treating TB.

The most common reason(s) for patients remaining infectious during treatment are the non-adherence to therapy and the presence of drug-resistant organisms. For patients who have MDR-TB, continued isolation throughout the period of hospitalisation should be

strongly considered (regardless of the above factors) because there is a tendency for treatment failure and/or relapse in these cases.

In general, patients who may be infectious at the time of discharge should not be discharged to new social circumstances—such as to previously unexposed contacts or new accommodation—or to an environment in which there are young children under 5 years of age.

6.4.2 Hospital Discharge of Patients

At the time of hospital discharge, patients should be provided with:

- A clear plan for outpatient follow-up, including an outpatient appointment with the appropriate medical officer
- Sufficient medication to cover the period until the outpatient appointment
- Confirmation that the patient has been notified to the Department of Human Services as having TB and that appropriate follow-up Departmental nursing arrangements have been made.

6.5 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 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* (see Section 6.3.3). Such patients should be identified at the time of presentation, triaged to the isolation area and given a surgical mask(s) to wear. They should be instructed to keep their masks on and cover their mouths and noses with disposable tissues when coughing or sneezing, until a clinical decision about the likelihood of TB is made.

Patients with confirmed or suspected active TB must be managed away from those patients known to be infected with HIV. Institutions should ensure they have strategies so that patients with confirmed or suspected active pulmonary TB attending outpatient appointments can be assessed away from the general outpatient population.

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7. Preventing TB Infection and Disease among Health Care Workers

7.1 Introduction

In the first half of the twentieth century, Australian nurses and doctors experienced relatively high rates of TB infection and disease. The control of TB in the second half of the century led to the closure of sanatoria, and a shift of care of TB patients to the general hospitals and community. Vaccination of tuberculin-negative health care workers with Bacille Calmette-Guerin (BCG) vaccine was nearly universal through this period. The effectiveness of hospital infection control and the incidence of latent TB infection of health care workers during this time are largely unknown.

The resurgence of TB in the United States in the 1990s, including reports of health care workers infected with drug-resistant TB, focused attention on improved clinical and microbiological strategies to identify TB cases quickly, and engineering strategies to reduce airborne transmission of TB. Early identification, isolation, diagnosis and treatment of TB cases should reduce infection of health care workers by reducing their chance of exposure to an undetected, untreated, infectious case of TB in the hospital.

A tuberculin skin test survey in Melbourne hospitals in the 1990s (Stuart et al., 2001) suggests TB infection of health care workers continues to occur despite the decline of TB in the community. Employees involved in direct patient care had a higher prevalence (19.3 per cent) of positive tests than had other employees (13.7 per cent). The prevalence of positive tests was highest among nurses. The study also found a higher prevalence of positive TST among employees of hospitals that lacked negative pressure isolation rooms. The study identified the need for hospitals to have TST screening programs and sufficient negative pressure isolation rooms for the number of suspected and confirmed TB cases at the institution.

The prevalence of positive TST describes the cumulative risk of TB infection through life and employment; few data are available to estimate the current annual risk of TB infection of health care workers. Limited recent local data on health care workers whose serial TST had converted (a marker of recent infection) would suggest that new infections are now relatively uncommon (Stuart et al., 2001).

The relative merit of programs based on regular screening by TST, compared with routine BCG vaccination, has been debated. Different personal and institutional costs and benefits accrue from the two approaches. There are no relevant contemporary local data on the efficacy of BCG vaccine in health care settings. The Centers for Disease Control and Prevention (2000) recently published evidence-based guidelines for TST screening and the treatment of latent TB infection.

7.2 Occupational Health and Safety Legislation—Duty of Care of Employers and Employees

The Victorian *Occupational Health and Safety Act 1985* defines the duty of care of employers as being to 'provide and maintain so far as is practicable for employees, a working environment that is safe and without risks to health'. This duty extends to patients, visitors, contractors and others who enter or use 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.

7.3 Strategies for Health Care Institutions

This chapter provides strategies to help health care institutions (1) address their obligation to minimise the risk of TB to health care workers and (2) identify health care workers infected with TB and initiate appropriate care. The following strategies apply to all workers, students and volunteers in health care settings, including those in long term care facilities and community-based care:

- Written policy and demonstrable processes relating to health care workers and TB
- A TB education program
- Assessment of the risk of TB to the institution and health care worker groups
- Tuberculin skin testing of health care workers
- Contact tracing and reactive tuberculin skin testing of health care workers exposed to TB cases
- Isolation in appropriately ventilated rooms of suspected and known TB cases, and personal protection of health care workers
- BCG vaccination
- Compliance and accreditation.

7.3.1 Written Policy and Demonstrable Processes

Health care institutions must have a written policy and demonstrable processes to prevent and monitor TB infection among staff, students, volunteers and contactors. They must develop policies and procedures to address the above strategies in the particular circumstances of the institution, in consultation with staff and occupational health and safety representatives, and in response to the regular reviews of the TB risk to health care workers.

7.3.2 TB Education Program

The *Occupational Health and Safety Act 1985* defines the duty of an employer as being 'to provide such information, instruction, training and supervision to employees as are necessary to enable the employees to perform their work in a manner that is safe and without risks to health'. Institutions, therefore, must provide a TB education program that is appropriate to their particular circumstances. A suitably qualified person (such as an infection control practitioner or a physician with experience with TB) should prepare this program, which should be delivered to all staff, students and volunteers during their induction, including staff employed on a sessional/casual basis.

Education should cover the following

- The mode of transmission of TB infection
- The natural history of TB infection
- Clinical and epidemiological features of TB disease
- The importance of prompt identification and isolation of persons suspected or known to have infectious TB
- Engineering and personal protective strategies available to prevent nosocomial transmission of TB
- The role of tuberculin skin testing of staff
- Procedures for contact tracing, referral, treatment and counselling of health care workers infected with TB during their employment
- The institution's policies and procedures for TB management, prevention and control.

Areas within institutions that may be at greater risk from TB must address their particular circumstances and infection control processes in their staff TB education program. These areas include, but are not limited to, accident and emergency departments, intensive care units, respiratory wards/units and endoscopy units. Institutions must also provide regular in-service education about TB. Updates may address trends such as the admission of TB cases, the delay to isolation of cases, compliance with tuberculin skin testing and TST conversion rates.

7.3.3 Assessment of the Risk of TB

The purpose of TB risk assessment is to guide TB control strategies, particularly the need for, and frequency of, regular TST screening (see Section 7.4). 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 isolation facilities for airborne diseases
- Evidence of recent TB infection of health care workers, based on serial TST
- Populations served by the institution.

Institutions with evidence that they admit, on average, less than one patient with infectious TB per year may be considered to have a low TB risk (Stuart et al., 2001; Field 2001).

Health Care Workers' 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 health care workers within the institution. Prospectively measured local rates of TST conversions in different groups of health care workers are much needed. Until such data become available, the following risk categories may serve as a guide to the risk to particular groups.

High risk settings (annual tuberculin skin testing) include:

- Respiratory wards, clinics, laboratories, bronchoscopy theatres
- Intensive care units
- Emergency departments
- In-patient and out-patient settings where persons with TB or HIV infection are cared for or investigated
- Laboratories dealing with potentially tuberculous material (mycobacteriology, bacteriology, histology and cytology)
- Mortuaries.

Medium risk settings (two-yearly tuberculin skin testing unless annual incidence of conversion is less than 1 per cent) include:

- All other settings where direct patient care is provided, but that are not listed as 'high risk' (including those with medical, nursing, physiotherapy, paramedical and non-clinical ward staff)
- Community settings in which health care workers may face an increased risk of exposure to TB (for example, persons who are being treated for TB, homeless, drug users or recent migrants from countries where TB is common)
- Ambulance service
- Paediatric hospitals.

Low risk settings (entry and exit tuberculin skin testing only required) include:

- Settings where staff have no contact with patients or their clinical specimens, such as the kitchen and administrative areas.

Significantly immunocompromised health care workers must not be exposed to settings known or suspected to pose a risk of TB infection.

Regular Review of TB Risk

Institutions must regularly review:

- Their incidence of TB admissions
- The effectiveness of their TB infection control strategies (including diagnostic delays and the use of isolation facilities)
- Compliance with tuberculin skin test screening
- Annual TST conversion rates
- The results of follow-up of health care workers exposed to cases of TB.

They must provide these data annually to staff, their occupational health and safety representatives, and the institutional occupational health and safety committee.

7.3.4 Protocols for Tuberculin Skin Testing of Health Care Workers

The institution must provide TST screening to staff freely, confidentially and at the employer's expense. Screening is preferable on site, although an appropriate external provider is an alternative.

Tuberculin skin testing of health care workers aims to:

- Promptly identify all health care workers infected with TB at the start of their employment and during their employment.

- Prevent health care workers infected with TB progressing to TB disease.
- Establish the tuberculin status of health care workers as a point of reference for future TST.
- Quantify the risk to health care workers of TB infection.
- Identify settings with increased risk to health care workers of TB infection, take steps to reduce this risk, and monitor the effect of the intervention.

Entry Testing

- All medical, nursing, non-clinical general ward and clinic, pathology, radiology, dental, mortuary and paramedical staff should undergo tuberculin skin testing before or within four weeks of commencing employment. Offer the test to health care workers who are already employed but do not have a record of their tuberculin status.
- 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.
- Persons with a first TST of less than 10mm 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. Subsequent regular tests (if indicated) involve only a single TST.
- The yield from two-step testing is likely to be low in young health care workers who have never been vaccinated with BCG or have not lived or travelled in countries of high TB incidence. Two-step testing need not be performed if the initial test is greater than 9 mm.
- Entry testing may be waived if the health care worker can provide a record of having undergone a TST within the previous three months.
- The institution must provide a written explanation to staff about the TST program, including the recommended frequency of testing and the contact details of testing personnel.
- Persons with an unexplained positive TST - typically tests 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 assessment and support.
- Pre-employment chest x-rays are necessary only if clinically indicated.

Exit Testing

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

Regular Testing

Whether and how often regular TST screening is undertaken during employment depends on the institutional TB risk, and the risk to particular health care workers of TB infection. Institutions that admit, on average, less than one patient with infectious TB per year, do not need to perform regular TST testing of staff (see Chapter 8, 'Preventing TB in Institutions', for information relating to nursing homes, hostels and special accommodation facilities).

Institutions that admit, on average, one or more patients with infectious TB per year should base the frequency of regular TST on the actual risk of infection, as determined by regular TST. In typical larger regional and metropolitan hospitals, several years of regular TST of high and medium risk staff provide an initial estimate of the incidence of infection. In the absence of such evidence, institutions may base the frequency of testing on the estimated risk posed by the particular work setting (see Section 7.3.3).

- Regular tuberculin skin testing of health care workers in paediatric institutions in Victoria is unlikely to be worthwhile.

Health Care Worker Setting	Frequency of Regular Tuberculin Skin Testing
High risk	Annual
Medium risk	Every two years, unless the risk of infection is less than 1 per cent per year.
Low risk	Not required

- A one-step TST is sufficient for regular testing of persons with a documented previous two-step TST.
- Tuberculin skin testing is contraindicated in persons with previous strongly positive tests or previously established TB infection or disease, and 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 results with periodic tests. For such persons, the discomfort of periodic tests may outweigh the diagnostic usefulness of periodic testing, and it may be prudent to reserve TST of such persons for the follow-up of high risk exposures.
- Persons with test increases of more than 10 mm (that is, a conversion) and persons with a test of greater than or equal to 15mm (if they are known to have had BCG) or greater than or equal to 10mm (in the absence of a BCG scar) should be referred for assessment and support.

Institutional Records of Tuberculin Skin Tests

Institutions must securely and retrievably store institutional records of TST, referrals, investigation and treatment, and maintain confidentiality between the test provider and the health care worker. This process must allow for access to records to follow up TB exposure and for de-identified aggregate data for routine regular reviews of conversion rates.

Institutions must provide each health care worker with a regularly updated personal record of their tuberculin status, BCG vaccination details, chest x-ray reports and details of treatment of latent TB infection, to take from workplace to workplace (see, for example, the wallet-sized Department of Human Services Health Care Worker Personal Immunisation Record). There must be a process for providing a copy of the TST record, referrals, investigation and treatment to a nominated person at the health care worker'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.

7.3.5 Contact Tracing and Reactive Tuberculin Skin Testing of Health Care Workers Exposed to TB Cases

If health care workers are 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 while after admission, and infection control measures for suspected and known TB cases were not used.

Contact tracing within the health care institution requires a written contact tracing protocol, including or identifying 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, students, volunteers and contractors exposed to the TB case.
- Provide written advice to exposed persons, including details of their TST appointment (typically eight to 12 weeks after their last exposure to the case).
- Provide a TST immediately after exposure to persons with no record of a previous TST. These persons then require another TST approximately 12 weeks later (unless the initial test is strongly positive).

- If a person has no record of a TST in recent years, then an immediate post-exposure TST and another 12 weeks later will provide better evidence of recent infection.
- An immediate post exposure TST is often not possible when the diagnosis of TB (typically by culture) is made four or more weeks after the last unprotected exposure of the health care worker. In such circumstances, a single TST ten to 12 weeks after the last exposure is the only feasible strategy. The results of such TST may be difficult to interpret unless a record of an earlier skin test is available.
- Perform and document TST of exposed staff and explain the test result to staff. Staff self-reading of tests is unacceptable.
- Counsel persons with a TST conversion (increases by greater than 10 mm) or new strongly positive TST (greater than or equal to 15 mm), and refer them to an appropriately qualified clinician for assessment.
- Trace and complete follow-up of persons who miss their follow-up TST appointment.
- Review and summarise the incident and follow-up, and provide feedback to the infection control unit, occupational health and safety committee and affected staff.

7.3.6 Isolation of Suspected and Known TB Cases, and Personal Protection of Health Care Workers

The identification and isolation of suspected and known cases of TB are described in Chapter 6, 'Hospital Care of TB'. Persons suspected or known to have infectious TB must be promptly placed in, and restricted to, clearly labelled airborne disease isolation facilities. The contact of staff, students and volunteers with persons suspected or known to have infectious TB should be restricted to strictly necessary encounters. All persons entering an isolation room should wear an appropriate sub-micron mask (see Chapter 6, 'Hospital Care of TB').

7.3.7 BCG Vaccine

The role of BCG vaccine in managing the TB risk to health care workers is contentious. There is no evidence that BCG reduces the chance that a health care worker exposed to an infectious TB case becomes infected as a result of the exposure. Once a person is infected, BCG may (or may not) influence the natural history of TB by reducing the risk of progressing to disease. A healthy non-BCG-vaccinated health care worker recently infected with TB has an approximately 10 per cent lifetime risk of progressing to TB disease. Estimates of the degree to which previous BCG vaccination may reduce this risk of progression vary from 0 per cent to 80 per cent (Brewer, 1995 and 2000; Colditz, 1994; Iseman 2000). Data on BCG vaccination's likely benefit and risk reduction for healthy health care workers in the contemporary developed world are scant, but risk reduction may be approximately 50 per cent.

The possible benefits of BCG vaccination of health care workers 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 has the theoretical benefit of providing an immunological defence against the development of TB disease from strains of *M. tuberculosis* that may be resistant to antibiotics used to treat latent TB infection.

The possible problems of BCG vaccination of health care workers are that:

- BCG confounds the interpretation of the tuberculin skin test and precludes the test from being used to diagnose TB infection in many BCG recipients.
- Health care workers who are latently infected with *M. tuberculosis* may not receive treatment, because there is a lack of screening or diagnostic confusion.

- BCG may act as a disincentive for health care workers to participate in regular tuberculin skin testing, by conferring a false sense of protection against infection.
- The institution may be unable to use regular tuberculin skin testing to assess the efficacy of TB infection control.

An institution should consider offering BCG vaccination to health care workers where the risk to those workers of repeated exposure to infectious TB cases is high and not controlled (as shown by ongoing tuberculin skin test conversions) despite appropriate infection control practices (see Chapter 9, 'BCG Vaccination'). But, BCG vaccination should not be administered to health care workers who are immunocompromised, infected with HIV, pregnant or likely to become pregnant soon.

Some BCG-vaccinated health care workers still can be monitored by regular tuberculin skin testing, but many will have or develop tuberculin reactions in excess of 10 mm. In the latter case, further tuberculin skin testing will be relatively or absolutely contraindicated.

7.3.8 Compliance and Accreditation

All health care institutions must meet the accreditation standards and guidelines of various State and Commonwealth government departments and agencies. Compliance will help health care institutions meet their legal responsibilities under occupational health and safety legislation and relevant accreditation standards.

The view of the Department of Human Services is that the board of governance is responsible for providing a safe environment for patients, staff and visitors. In August 2000, all health services and hospitals were required to submit an Infection Control Strategic Management Plan to the Department, outlining the key priority areas for infection control and prevention over the next three years. One of the five priority outcome areas to be included in the plan is to 'Protect health care workers and visitors'. In this area, key performance measures include:

- The organisation's capacity to provide all employees with screening and immunisation based on the Department's *Immunisation Guidelines for Health Care Workers*
- The institution of policies and procedures for the evaluation of exposed or infected staff
- The capacity (number and mix of isolation rooms) and personal protective equipment provided to isolate patients with airborne, antibiotic-resistant or communicable diseases that reflect the casemix, disease risk and services provided
- The incorporation of the *Guidelines for Isolation Rooms* in all planning for new or refurbished isolation facilities.

Hospitals will be required to report to the Department annually on their progress in implementing the plans.

A State-wide survey of all Victorian public hospitals to evaluate the effectiveness of current infection control programs will assess the extent to which the hospitals have facility-wide programs in place to prevent communicable and infectious diseases, such as staff vaccination/screening programs, the maintenance of staff vaccination/screening/exposure databases, adherence to staff vaccination guidelines, staff infection control education, and the dissemination of information on isolation room availability, use and design. Health services and hospital boards are not only held responsible for ensuring appropriate infection control programs are in place; health services also will report to their communities annually on their infection control plans and performance as part of their Annual Quality of Care Reports.

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8. Preventing TB in Institutions

8.1 Introduction

Residents of aged care facilities, special accommodation hostels, prisons and homeless shelters are at increased risk of becoming infected with TB. Awareness of the possibility of active TB disease is the cornerstone of preventive measures in these institutions. Risk is significantly increased by factors that include:

- Age
- Alcoholism
- HIV infection
- Injecting drug use
- Diabetes
- Silicosis
- Malnutrition and cachexia
- Immunosuppression due to medication such as steroids.

Tuberculin skin testing has a low predictive value in the elderly and other immunosuppressed groups, and should not be relied on for diagnosis of suspected disease. In the settings listed above, a delay in diagnosis, sustained contact with the index case, inadequate ventilation or overcrowding can contribute to the risk of TB transmission.

8.2 Administrative Controls

Institutions can limit the transmission of TB infection by having adequate controls in place, including:

- Effective written policies and protocols to ensure the rapid identification of persons likely to have TB
- Protocols that require physicians admitting to nursing homes, hostels and special accommodation facilities to undertake and report a pre-admission medical assessment, including the resident's previous history of TB, history of cough and baseline chest x-ray where appropriate
- Education, training and counselling of health care workers about TB (see Chapter 7, 'Preventing TB Infection and Disease among Health Care Workers')
- Guidelines for procedures to be followed in the event of a TB diagnosis.

The latter guidelines should include the following:

- The institution should transfer persons with suspected or active TB to an appropriate acute care facility until therapy is initiated and the patient is stabilised (see Chapter 6, 'Hospital Care of TB').
- Persons likely to have TB must be investigated and treated early.
- The institution must undertake immediate contact investigations where a resident has suspected or known TB (see Chapter 16, 'Contact Tracing').
- The institution must liase with the treating physician at the acute care facility to ensure the discharge criteria for ending TB isolation are met, before allowing the patient's return to the pre-admission facility.
- The institution must ensure adequate supervision of patients on anti-TB treatment to maintain compliance with therapy.

Health care workers involved with these high risk groups must maintain a high index of clinical suspicion about the possibility of active TB disease, and the appropriate clinical investigations must be undertaken as indicated (chest x-ray, sputum smears and culture, and tuberculin skin testing where appropriate). Recent examples of unrecognised active TB disease, leading to new infection and the need for mass tuberculin testing of large institutional communities, underline the importance of the need for particular vigilance by medical officers and other health care workers in institutions such as prisons and nursing homes. The possibility of TB infection should be kept in mind for any person who presents with complaints of cough, weight loss, haemoptysis and/or sweats.

Screening chest x-rays are not cost-effective and cannot be recommended, except where there is specific clinical indication or where other measures such as treatment of latent TB infection or TST screening (in the immunosuppressed, for example) are unlikely to be effective.

8.3 HIV in the Prison Population

HIV infection has a direct impact on TB because HIV co-infection is the most serious risk factor for developing TB disease. Screening HIV-positive inmates of a prison for latent TB infection identifies those who would benefit from the treatment of latent TB infection. A HIV-positive inmate with possible symptoms of active TB should be isolated and evaluated despite a negative TST and a clear chest x-ray.

Any therapy—either treatment of latent TB infection or treatment of active disease—given to any person in these high risk groups should be fully supervised. Where clinically indicated, a chest x-ray is the most effective screening procedure in this context, followed by sputum smears and culture for confirmation.

Further Reading

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9. BCG Vaccination

9.1 Introduction

BCG vaccination has been undertaken on a regular basis in Victoria since 1950, with the intended purpose of improving community resistance to TB. The aim of the BCG vaccination program for school leavers in the 1950s was to improve the levels of 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. When this program commenced in 1950-52, TB was a leading cause of death (about 30 per cent) for those aged 20-40 years old in Australia.

The school leaving-age vaccination program was terminated in 1984-85 following a review of TB incidence patterns in Victoria over the previous 30 years in the Australian and overseas-born population aged 15-29 years old. The Victorian incidence patterns were compared to those for equivalent age groups in New South Wales, where BCG vaccination had not been used since 1950. New South Wales thus acted as a control for the school-leavers program routinely undertaken in all other Australian States and Territories. No significant long term protective effect from BCG could be demonstrated in the Victorian Australian-born population by 1980 (Monheit, 1985).

Since 1985, there has been a progressive reduction in the incidence of TB in the Australian-born population (now generally less than 1 per 100,000 in adolescents and young adults), but TB continues to have a considerable impact on the overseas-born Australian population. There is little (if any) evidence, however, of a significant transmission of infection between the overseas-born and Australian-born populations.

Various studies around the world have critically reviewed BCG vaccination—the most notable being the meta-analysis by Colditz et al. (1994), which concluded 'on average, BCG vaccine significantly reduces the risk of TB by 50 per cent'. While recognising that BCG vaccination does not prevent TB, the study also noted that the vaccine gives protection 'of the order of approximately 80 per cent' against death from the more severe forms of TB (namely, miliary TB and tuberculous meningitis) in the most susceptible population groups studied (namely, newborns and young children).

BCG vaccine, being a freeze-dried live vaccine, is contraindicated in the management of HIV-associated TB or its prevention, given the increased risk of disseminated BCG infection. BCG vaccination is also contraindicated in persons who are suffering from other forms of immunosuppression and persons who are pregnant or likely to be pregnant soon. In a developed industrialised society such as Australia, particularly in Victoria, there is no evidence that the use of BCG vaccination in an adult population usefully contributes to TB control, other than in specific instances such as persons exposed to multidrug-resistant TB (MDR-TB) or immunocompetent persons working in high risk settings.

Further, because the rationale for BCG vaccination is to introduce an attenuated non-virulent form of *M. bovis* into the body system, thereby initiating a cell-mediated immune response, BCG vaccination has the unwanted side-effect of inducing tuberculin conversion in a large proportion of those persons vaccinated. This tuberculin conversion can persist, to varying degrees, for many years. Current opinion suggests that the protective effect of BCG vaccine persists for approximately nine to 10 years. Consequently, the results of tuberculin skin testing are frequently distorted and the interpretation of these tests is made difficult in contact surveys to detect the presence of tuberculin conversion.

The National Health and Medical Research Council reviewed the place of BCG vaccination in Australia. Its current recommendations are published in the latest revision of *The Australian Immunisation Handbook*. The handbook's Section 3.26, 'Tuberculosis', contains details of available vaccines, transport, handling and storage, administration techniques and adverse reactions.

BCG vaccine is made available to vaccinators authorised by the Department of Human Services. Vaccinators will be authorised only after undertaking a course of instruction conducted by the TB Program, to familiarise them with the procedures, risks, contraindications and adverse effects of both TST and BCG vaccination. Renewal of authorisation depends on the demonstration of a continuing need for involvement in BCG vaccination activities.

9.2 Indications for BCG Vaccination

Having regard for 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**. It is recommended, however, in the following groups of infants and young children:

- Aboriginal neonates in remote regions of Victoria where an increased incidence of TB has been demonstrated in that community
- Infants born to persons suffering from leprosy
- Children under the age of 5 years who will travel to live for more than brief periods (four to six weeks) in countries of high TB prevalence (defined by the World Health Organisation as countries with an annual incidence of TB of greater than 100 per 100,000 population)
- Infants and young children under the age of 5 years who live in a household that includes immigrants or unscreened visitors who recently arrived from countries of high TB prevalence. This group includes infants and young children in families that travel frequently to visit or stay in the homes of relatives in countries of high TB prevalence.

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

- Children and adolescents aged less than 15 years who continue to be exposed to an index case with active smear and/or culture-positive pulmonary TB, and who cannot be placed on isoniazid preventive therapy
- Children, adolescents and young adults to the age of 25-30 years who have been exposed to an index case with active MDR-pulmonary TB (where the organisms are resistant to at least both rifampicin and isoniazid).

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

- Health care workers 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 who are likely to be exposed to active cases of MDR-TB (see Chapter 7, 'Preventing TB Infection and Disease among Health Care Workers'). **Note: BCG vaccination is no longer routinely recommended for health care workers in Victoria.**
- Persons aged over 5 years through to young adulthood who are living or travelling for extended periods (two to three months or more) in countries of high TB prevalence.

9.3 Contraindications to BCG Vaccination

BCG vaccination is contraindicated in the following clinical situations:

- The individual has demonstrated a positive TST of greater than 5-mm diameter induration.
- The individual is immunocompromised. This category includes those with known or suspected HIV infection (those at high risk and with unknown HIV antibody status), those on corticosteroid or other immunosuppressive therapy, radiation or chemotherapy, or those with malignancies involving either bone marrow or lymphoid systems. All these individuals are at greatly increased risk for disseminated BCG infection.
- The individual is pregnant or likely to be pregnant soon. There is no evidence of BCG causing foetal damage, but the use of live vaccines is not recommended during pregnancy.
- The individual is known to have had TB disease in the past.
- The individual is febrile.
- The individual suffers from a generalised skin disease such as eczema and psoariasis.

9.4 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. Occasionally, anaphylactoid reactions can occur, but they are rare. The most common adverse reaction is the development of a localised abscess at the site of injection, especially if the vaccination is given too deeply.

Accelerated BCG responses are seen when an already TST positive individual is vaccinated with BCG. These exaggerated responses usually develop within five to seven days of vaccination and often result in gross local reactions and axillary lymphadenopathy. Unsightly keloid scars can result from vaccination, with or without an accelerated response. Very rarely, a potentially fatal disseminated infection can occur in an immunocompromised individual who has undergone BCG vaccination.

When adverse reactions require treatment, the infective process usually can be rapidly suppressed with a combination of isoniazid and rifampicin in standard doses taken for two to four months, depending on the individual situation. (BCG, being derived from *M. bovis*, is naturally resistant to pyrazinamide.)

9.5 Availability of Vaccine

Supplies of tuberculin and BCG vaccine are available free of charge through the Communicable Diseases Section, Department of Human Services. Contact the Vaccines Officer on (03) 9637 4144 or fax (03) 9637 4186. Supplies of BCG vaccine will be made available to only authorised vaccinators.

Where BCG vaccination is recommended as part of specific TB control activities, this information is to be recorded. The individual being vaccinated (or, if a child, their parent/guardian) is to be provided with written details of the results of TST and confirmation of the BCG vaccination. Where BCG vaccination is undertaken for other indications, the personal details and indication for vaccination are to be supplied to the Department's Communicable Diseases Section before the BCG vaccine is issued. The individual being vaccinated should receive appropriate written confirmation, including the details of the tuberculin skin test. Authorised BCG vaccinators must ensure they are fully conversant with the risks, procedures, adverse effects and contraindications of BCG vaccination as detailed in the current edition of *The Australian Immunisation Handbook*.

9.6 Conclusion

The general use of BCG vaccine in Victoria is no longer recommended. BCG vaccine is to be used only in specific cases where risk factors can be clearly identified either in the general community or in specific occupationally exposed groups. Where uncertainty arises regarding the appropriateness of BCG vaccination in an individual, please contact the Nurse Manager, TB Program—email lynne.brown@dhs.vic.gov.au, telephone (03) 9637 4110 or fax (03) 9637 4477—who can refer to appropriate consultant advice where necessary.

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10. Treatment of Latent TB Infection (Preventive Therapy)

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 TST or QuantiFERON-TB response (especially if the latter is positive for more specific antigens such as ESAT-6 or CFP-10), the aim of therapy is to reduce the risk of progression to active TB disease. The intention is to reduce the intra-cellular bacillary load to low levels that the immune system can more easily control. The benefits of treatment for latent TB infection, however, need to be carefully weighed against the risks of drug toxicity and/or the risks of poor treatment compliance resulting in the emergence of drug resistance, especially if combination regimens are used.

Since the 1950s, it has been standard practice to use isoniazid alone. A number of literature reviews indicate that isoniazid used as a single drug for six to 12 months (optimum nine months) on a daily or intermittent basis in an appropriate dose (5–10 mg/kg to a maximum of 300mg 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.

In situations of impaired immunity, the use of isoniazid needs to be prolonged for at least 12 months and possibly for life, especially with advanced HIV/AIDS infections with markedly reduced CD4+ lymphocyte counts. Treatment of latent TB infection using two or more agents for much shorter periods of two to four months (for example, isoniazid and rifampicin, rifampicin and pyrazinamide, or pyrazinamide and a fluoroquinolone such as ciprofloxacin or ofloxacin) can be considered for cases involving exposure to drug-resistant sources or for cases with HIV co-infection. Evidence of long term effectiveness is not as strong for these combinations, especially in immunocompetent individuals, and the risk of potentially serious hepatic intolerance appears to be much greater.

Drug toxicity leading to hepatitis is a major drawback of combination therapy, and close screening of liver and renal functions is desirable, certainly for the first six to eight weeks and often for extended periods depending on the individual's clinical situation. The late development of hepatic toxicity going on to hepatic failure, at times requiring liver transplantation, is a well-recognised and potentially fatal complication.

Compliance with treatment is essential for a useful long-term effect. (At a minimum, at least 80 per cent of the intended dose should be consumed.) If it is not possible to ensure compliance, it is preferable not to give treatment for latent TB infection. Where combination treatment is given, then *FULLY SUPERVISED TREATMENT is ESSENTIAL* to minimise the risk of later emergence of resistant strains. The preservation of rifampicin sensitivity is so important to global TB control that an argument could be made for restricting rifampicin-containing treatment regimens for latent TB infection to only those persons who have a specific indication, such as HIV-positive individuals and those exposed to multidrug-resistant TB (MDR-TB).

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.

References

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Joint Tuberculosis Committee of the British Thoracic Society. 'Control and prevention of tuberculosis in the United Kingdom: Code of Practice 2000'. *Thorax* 2000; 55: 887-901.

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11. HIV Infection and TB

11.1 Importance

Globally, TB is the most important opportunistic infection complicating HIV infection. An estimated 20 million people are co-infected with HIV and *M. tuberculosis*, and 15 per cent of the world's estimated nine million cases of TB each year occur in HIV-infected people.

Dual infection with HIV and *M. tuberculosis* is much less common in Australia than in developing countries. Less than 5 per cent of Australian AIDS patients develop active TB, most of whom were born or travelled extensively in TB-endemic countries.

TB 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 health care workers as well other HIV-infected patients) have occurred overseas, some inving multidrug-resistant TB (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 will develop TB each year—a risk that is four to 25 times higher than the risk for those without HIV infection. HIV-infected patients who become newly infected with *M. tuberculosis* are also much more likely to develop symptomatic primary infection. TB also has an impact on the course of HIV infection. In vitro, cytokines released in response to *M. tuberculosis* infection enhance HIV replication. HIV-infected patients with TB in developing countries develop more opportunistic infections than developed by patients who are at a similar stage of HIV infection but do not have TB.

11.3 Clinical Manifestations

The clinical presentation is influenced by:

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

Patients with relatively well-preserved immunity and pre-existing latent TB infection usually present with pulmonary TB and manifest the typical clinical, radiological and microbiological findings. In contrast, HIV-infected patients with primary TB and those with reactived TB and impaired immunity (a CD4 cell count of less 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 the absence of cavitation, infiltrates in the mid and lower zones, and hilar lymphadenopathy.

11.4 Diagnosis

11.4.1 Latent TB Infection—Tuberculin Skin Test

Tuberculin skin testing should be part of the routine evaluation of every newly diagnosed HIV-infected person. The interpretation of the tuberculin skin test is complicated by the decline in cell-mediated immunity that accompanies HIV infection. For this reason, and because the risk of progression from latent to active TB infection is so high in HIV-infected people, a Mantoux test reaction of 5 mm or greater is considered to indicate infection with *M. tuberculosis.* This cut-off can be raised to 10 mm for patients with a CD4 cell count greater than 500 per microlitre and a past history of BCG vaccination.

Skin testing with control antigens that elicit a delayed type hypersensitivity response may help the interpretation of a negative tuberculin test, but such testing has never been widely employed in Victoria.

11.4.2 TB

The possibility of TB must at least be considered in any HIV-infected patient presenting with a pulmonary infiltrate, and should be strongly suspected in the presence of epidemiological risk factors or clinical features such as sub-acute or chronic symptoms, weight loss or haemoptysis. Occasionally patients with pulmonary TB have a normal chest x-ray, but this is most unusual. Any patient with acid-fast bacilli visible in a sputum specimen must be assumed to have TB (and not disseminated *M. avium* complex infection) and should be managed accordingly, pending sputum culture results.

M.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.

11.4.3 Unsuspected HIV Infection

TB is occasionally the initial manifestation of unrecognised HIV infection, because TB may occur with relatively well-preserved immune function. All patients with newly diagnosed TB should be asked about HIV risk factors, and there should be a low threshold for advising patients to undergo HIV testing (after appropriate counselling).

11.5 Prevention

All patients with a positive tuberculin skin test, as previously defined, should be assessed for active TB by history, examination and chest X-ray. Patients with no evidence of active disease should be strongly considered for treatment of latent TB infection, with a course of isoniazid for nine months. (Short course treatment of latent infection with rifampicin and pyrazinamide for two months is as effective as isoniazid.) Given the very high risk of progression to active disease in these patients, age of 35 years or more is not a contraindication to treatment of latent infection.

For HIV-infected contacts of a patient with smear-positive pulmonary TB, isoniazid is strongly advised for those with a positive tuberculin skin test (regardless of age) and may even be considered for those with a negative test. BCG is contraindicated in HIV-infected persons.

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

11.5.1 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 TB'.

11.6 Treatment

The treatment of TB in a HIV-infected patient is not straightforward, chiefly as a result of the complex interactions between anti-retroviral, anti-tuberculous and other drugs. Only a doctor(s) with special expertise in HIV medicine and TB should manage patients with TB who are HIV infected. If more than one doctor is involved, then close cooperation is essential to ensure optimal treatment coordination.

11.6.1 Anti-Retroviral Drugs

The three major classes of drug are:

- Nucleoside reverse transcriptase inhibitors—zidovudine, didanosine, 3TC, stavudine, abacavir, zalcitabine
- Non-nucleoside reverse transcriptase inhibitors—nevirapine, efavirenz, delavirdine
- Protease inhibitors—nelfinavir, indinavir, ritonavir, saquinavir.

Modern anti-retroviral treatment employs a combination of anti-retroviral agents: usually two nucleosides and a protease inhibitor or a non-nucleoside agent. These regimens are referred to as highly active anti-retroviral treatment, or HAART.

11.6.2 Drug Interactions

Rifampicin is a potent inducer of hepatic cytochrome P450 3A4 enzymes, while rifabutin is less so. The protease inhibitors and delavirdine are cytochrome P450 3A4 inhibitors, nevirapine is an inducer, and efavirenz exerts mixed effects.

11.6.3 Regimens

No Anti-Retroviral Treatment

- The occasional patient not being treated with anti-retroviral agents should undergo a standard treatment regimen of isoniazid, rifampicin, pyrazinamide and ethambutol (see Chapter 4, 'Treatment of TB').
- Treatment duration for drug-sensitive infections is six months, unless the clinical or microbiological response is delayed, in which case treatment should be continued for at least four months after sputum becomes culture negative.

Drugs In Combination with Anti-Retroviral Treatment

- Isoniazid, ethambutol and pyrazinamide are used in standard doses.
- Rifabutin is used instead of rifampicin, at a reduced dose of 150 milligrams daily with indinavir, nelfinavir and saquinavir soft-gel capsules, and at a dose of 450 milligrams daily with efavirenz.
- Rifampicin is not generally recommended, although preliminary evidence suggests it may be possible to use with efavirenz or with ritonavir plus saquinavir.
- Treatment duration is six months, unless the clinical or microbiological response is delayed, in which case treatment should be continued for at least four months after sputum becomes culture negative.

11.6.4 Drug-Resistant Infections

These infections require longer courses of treatment, sometimes with non-first-line agents such as aminoglycosides or quinolones.

11.7 Monitoring

Monitoring should be as for non-HIV-infected patients. 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. Drug-induced hepatitis may be more common than in HIV-negative patients, however, so routine laboratory monitoring of liver function is recommended.

Reduced absorption of anti-tuberculous drugs has been demonstrated in some AIDS patients, but whether this contributes to a poorer treatment outcome is unclear.

11.7.1 Paradoxical Treatment Reactions

Patients who begin HAART and anti-tuberculous treatment at about the same time sometimes develop fever, lymph gland enlargement or a worsening pulmonary infiltrate several weeks later. This paradoxical reaction is probably due to a heightened immune response to *M. tuberculosis* secondary to HAART-induced immune reconstitution. The reaction usually resolves with time and anti-tuberculous treatment should be continued. Glucocorticoids can be used if the reaction is particularly severe or prolonged.

11.7.2 Post-Treatment

Although the recommended treatment duration is six months, some doctors continue treatment for nine or 12 months, or maintain the patient on indefinite isoniazid, especially for patients with very low CD4 cell counts who may be at higher risk of relapse. Reinfection with a different strain of *M. tuberculosis* after successful completion of TB treatment has been reported.

11.8 Outcome

Patients with drug-sensitive infections who adhere to their treatment regimen respond well to treatment, with failure and relapse rates comparable to those of non-HIV-infected patients. Widespread use of HAART 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.

Further Reading

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12. TB in Children and Adolescents

12.1 Introduction

TB in children differs markedly from that in adults. Many children acquire TB infection characterised by delayed hypersensitivity and few organisms, but relatively few develop TB disease. The risk of doing so, however, remains lifelong. While the initial infection in most children occurs in the lungs, TB in children and adolescents should be considered to be, at least potentially, a systemic disease. The primary complex comprising the site of infection and the involved regional lymph nodes may heal or complications may develop from the enlargement or rupture of the regional lymph nodes or the spread of tubercle bacilli into the bloodstream giving rise to disseminated disease. The risk of dissemination is greatest in the first five years of life and within the first 12-24 months after infection.

12.2 Risk of Disease Following Primary Infection

Data derived from UK studies of children followed for two years after infection in the 1950s and 1960s indicated that the risk of development of radiological changes in the chest consistent with TB infection were greatest in the first year of life and progressively decreased thereafter (Table 3).

Table 3: Risk of Disease Following Primary Infection

Age	Two-Year Risk
<1 year	23-43 per cent
1-5 years	11-24 per cent
6-10 years	8-25 per cent
11-15 years	16 per cent

For children who have a normal chest x-ray at the time a first positive tuberculin test is detected, the lifetime risk of developing TB disease is 2-10 per cent. These risks are related to the general health, nutrition and other disease states. In Australia, they are probably much lower than Table 3 suggests.

12.3 Infectivity

Childhood TB is rarely contagious because.

- Children with TB disease usually have a small bacterial load.
- Children rarely have cavitating disease.

Occasionally, mid-to-late adolescents are seen with cavities due to TB and they may be infectious.

12.4 Diagnosis

Diagnosis of TB infection is based on tuberculin skin testing. The interpretation of a positive test may be modified by the risk of infection and BCG vaccination status; thus, a positive test is an induration of:

- TST 5-10 mm in a child at high risk of infection and with no BCG vaccination
- TST 10-15 mm unless the child had BCG vaccination in the past
- TST > 15 mm unless the child had BCG vaccination within five years.

Some healthy adolescents and adults may have up to a 20-mm induration from a tuberculin skin test for up to five years after BCG vaccination.

Diagnosis of TB disease is based on clinical symptoms and signs, a chest-x-ray or other investigation, and a smear and culture of infected body material if this is available.

12.5 Treatment of Latent TB Infection

Children with TB infection and no evidence of TB disease are treated for latent TB infection for two reasons:

- First, to reduce the risk of disease developing in the years immediately after the infection is acquired, particularly in children under the age of 5 years old
- Second, to substantially reduce the lifelong risk of developing disease via the use of isoniazid therapy ideally for nine months. This therapy has few side effects in children and adolescents.

Nine months of isoniazid therapy should be considered, therefore, for otherwise healthy children and adolescents who have a positive tuberculin test (as defined above) and no evidence of TB disease. It is strongly recommended in the following risk groups:

- Ethnic communities with a high rate of TB
- HIV-positive people, in whom corticosteroid or immunosuppressive therapy is contemplated
- Diabetics and those with other chronic diseases, and people whose lifestyle or occupation may be associated with a higher incidence of TB
- Children under age 5 years old who have been in close contact with smear-positive active cases and who are tuberculin negative on initial screening, pending further review of their tuberculin status at three months from the 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.

Children who have a positive tuberculin test and who have radiological changes on a chest x-ray that are consistent with TB should be regarded as having TB disease and treated as such.

12.6 Treatment

Children with TB disease are usually treated with daily therapy with at least three drugs—isoniazid, rifampicin and pyrazinamide—for two months; then, generally, two drugs—isoniazid and rifampicin—are given for a further four months. Normally, these drugs are given daily, but three times per week therapy seems satisfactory. Such short course therapy (six months) has been shown to be effective in children with primary TB and with complicated primary TB limited to the respiratory tract, but there are insufficient data to recommend it for central nervous system, bone or joint TB infections. For these infections, 12 months of therapy is probably wise, and it is mandatory for the abovementioned at-risk groups.

13. TB and Pregnancy

13.1 Effect of Pregnancy on TB

Pregnancy has no adverse impact on TB if there is no great delay in diagnosis. Obstetric morbidity and perinatal mortality have been found to increase in patients whose treatment was started late in pregnancy.

The diagnosis of TB may be delayed in pregnancy. Pregnant patients with pulmonary TB are more likely to be asymptomatic at the time of diagnosis, compared with non-pregnant women with pulmonary TB (Carter and Mates, 1994). They also are more likely to have non-specific symptoms and to experience a delay in obtaining a chest x-ray (Doveren et al., 1998). The clinical manifestations of pulmonary TB, if present, are the same as in non-pregnant women. The tuberculin reaction is not altered in pregnancy.

The likelihood of extra-pulmonary TB is related more to the ethnic origin of the patient than to pregnancy. In Australia (and the United Kingdom), the incidence of extra-pulmonary TB is greater among immigrants than among those born in the country. The symptoms of extra-pulmonary TB are frequently non-specific and may be attributed to physiological changes of pregnancy. A high index of suspicion is needed when pregnant immigrants develop symptoms.

Infant and maternal mortality rates from untreated active TB are 30-40 per cent (Schaefer, 1975). With adequate treatment, a pregnant woman with TB has a prognosis equivalent to that of a comparable non-pregnant woman.

13.2 Effect of Pregnancy on Latent TB

The risk of disease developing in a tuberculin-positive pregnant woman with a normal chest x-ray is the same as the risk for a non-pregnant woman. The risk of reactivation of inactive pulmonary TB during the post-partum period is possibly higher, but this view is disputed.

13.3 Effect of TB on Pregnancy

In the pre-chemotherapy era, active TB in an advanced stage carried a poor prognosis for both the mother and the child. In the chemotherapy era, the outcome of pregnancy is rarely altered by the presence of TB except in the rare cases of congenital TB. Most studies have not shown that TB increases complications of childbirth. The general consensus is that the risk of an adverse pregnancy outcome is no greater among pregnant women on anti-tuberculous drugs than among healthy pregnant women. Untreated TB represents a far greater hazard to a pregnant woman and her foetus than does the treatment of her disease.

Congenital infection may occur as a result of transplacental spread or aspiration or ingestion of infected amniotic fluid in utero or 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.

13.4 Anti-Tuberculous Drugs in Pregnancy

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

Drug companies still recommend that *rifampicin* (category C) be avoided in pregnancy, but evidence regarding the teratogenicity of rifampicin is inconclusive. A high dose (150 mg/kg and over) is teratogenic in animals. The current consensus is that rifampicin is not teratogenic and that any risk to the foetus must be small compared with the risks from other sources. Pregnancy is not a contraindication of rifampicin.

Administered in later pregnancy, rifampicin can lead, in an unknown proportion of cases, to a haemorrhagic tendency in the newborn. (Some authorities prescribe supplemental vitamin K (10 mg/day for the last four to eight weeks of pregnancy.) There have been no reports of adverse

effects on breast-feeding babies whose mothers were taking this drug. Such babies will ingest less than 1 per cent of the normal therapeutic dose for infants and less than 0.1 per cent of the dose taken by the mother.

- The use of *pyrazinamide* (category B2) is little studied in pregnancy. If the patient is sick (for example, with tuberculous meningitis), then the drug should be used. Pyrazinamide is indicated:
- When multidrug resistance is suspected
- When the pregnant woman is HIV infected
- For tuberculous meningitis, especially when isoniazid resistance is a possibility.

Streptomycin (category D) occasionally causes ototoxicity and is contraindicated in pregnancy.

A *pyridoxine* supplement in pregnancy should be at a dose of 50 mg/day (instead of 25 mg/day).

13.5 Breast Feeding and Anti-Tuberculous Drugs

TB drugs get into breast milk. Breast-feeding infants receive no more than an estimated 20 per cent of the usual therapeutic dose of isoniazid for infants, and less than 11 per cent of other anti-tuberculous drugs. Potential toxic effects of drugs delivered in breast milk have not been reported.

To minimise the level of anti-tuberculous drugs in the newborn, the mother can take her anti-tuberculous drugs immediately after a feed and substitute a bottle for the next feed, then go back to her usual feeding pattern until the next day.

13.6 Management of the Newborn after Delivery

13.6.1 Mother's TB Is Likely to Be Associated with Haematogenous Spread or Active Genital TB

The following steps apply if the mother's TB is likely to be associated with haematogenous spread (for example, miliary TB, pleural effusion, tuberculous meningitis) during pregnancy or puerperium or active genital TB during that time:

- Consider that the infant has a definite risk of having or developing congenital TB. The onset of congenital TB averages two to four weeks (range: a few days to a few months).
- Assess for signs of congenital TB and treat with multiple-drug therapy if it is present.
- Separate the mother and child only if the mother is ill enough to require hospitalisation or if she is expected to be non-compliant and directly observed therapy is not possible.
- Conduct chest x-ray and gastric washings for smear and culture at birth. Lumbar puncture is indicated if there is suspicion of congenital TB.
- Conduct the tuberculin skin test at four to six weeks after birth (because it is likely to be negative at birth). Repeat the tuberculin skin test at 12 weeks and six months. Repeat the chest x-ray at four to six weeks. The tuberculin skin test is frequently non-reactive at the onset of clinical congenital TB.
- Repeat clinical evaluations, which are necessary for these high risk infants during the first six months.
- In the absence of active disease, commence isoniazid (10 mg/kg/day) at birth. Continue this for six months if the chest x-ray and tuberculin test remain negative. If the tuberculin reaction is greater than 5 mm, and there is no evidence of pulmonary and extra-pulmonary disease, then continue treating with isoniazid to complete a nine-month course. If the chest x-ray is abnormal, then regard it as evidence of congenital TB and treat accordingly. Some authorities would give both rifampicin and isoniazid from the outset.

13.6.2 Mother Has Active Pulmonary TB and Is Infectious

The following steps apply if the mother has active pulmonary TB and is infectious:

- Assess for signs of congenital TB and treat with multiple-drug therapy if it is present.
- Separate the mother and child only if the mother is ill enough to require hospitalisation or if she is expected to be non-compliant and directly observed therapy is not possible.

- In the absence of active disease, give isoniazid (10 mg/kg/day) to the newborn. Daily isoniazid can protect the newborn from acquiring TB.
- After four to six weeks of isoniazid, perform a tuberculin skin test and do a chest x-ray.
  (a) If the results are negative, then continue treating with isoniazid and repeat the test and x-ray at 12 weeks and six months.
  (b) If the tuberculin reaction is greater than 5 mm, then investigate thoroughly for pulmonary and extra-pulmonary disease. If evidence of disease is present, then treat with multiple-drug therapy.
  (c) If the tuberculin reaction is greater than 5 mm and there is no evidence of pulmonary and extra-pulmonary disease, then continue treating with isoniazid to complete a nine-month course. Some authorities recommend a 12-month course of isoniazid in this situation.
  (d) If the tuberculin reaction is negative and the chest x-ray is normal at six months (some would do this at 12 weeks), then discontinue treating with isoniazid if the mother is smear negative. If the family is from a high prevalence group for TB, then Victorian policy is to undertake BCG vaccination of the newborn.
  (e) If tuberculin reaction is negative and the mother is still smear positive, then this is a difficult situation. Investigate the mother for treatment failure, and exclude drug resistance. Continue treating the newborn with isoniazid unless isoniazid resistance is thought to be likely or confirmed; in the latter cases, give the newborn rifampicin and isoniazid. A strong case now exists for BCG vaccination.

The reason for repeating the tuberculin skin test at six months and giving isoniazid up to this time even if the reaction is negative is that tuberculin conversion may be delayed for up to six months in infants infected at birth.

- If BCG is given to the newborn, watch for an accelerated response (see document on BCG reactions). An accelerated response suggests that the newborn has been infected, therefore, appropriate investigation and management should be instigated. If there is no accelerated response, then conduct a tuberculin skin test two to four weeks later. A tuberculin reaction at this early stage suggests it is due to a natural infection and not to the BCG.

13.6.3 Mother Is Still on Anti-Tuberculous Treatment but No Longer Infectious

The following steps apply if the mother is still on anti-tuberculous treatment but is no longer infectious (that is, sputum culture is now negative):

- Do not separate the mother and child.
- Examine the infant at monthly intervals.
- Evaluate the TB risk in family members
- Conduct a tuberculin skin test at six weeks, 12 weeks and six months (see 13.6.1 & 13.6.2 for further action)
- Consider that there is a case for isoniazid preventive therapy for six months even if the mother is now sputum negative, because the mother (a) may have had haematogenous or genital spread, thereby infecting the infant, or (b) may sometimes (for example, during intercurrent respiratory infection) bring up enough tubercle bacilli to infect the infant.
- If the family is from a high prevalence group for TB, give the newborn a BCG vaccination, as per Victorian policy.

Some authorities feel that the mother, unless she has been culture negative for three months, should be regarded as potentially infectious and thus the newborn should be managed as discussed in Section 13.6.2.

13.6.4 Mother Completed Anti-Tuberculous Treatment during Pregnancy and Is No Longer Infectious

The following steps apply if the mother completed anti-tuberculous treatment during her pregnancy and is no longer infectious:

- Do not separate the mother and child.
- Evaluate the TB risk in family members.
- If the family is from a high prevalence group for TB, give the newborn a BCG vaccination, as per Victorian policy.
- If BCG vaccination is not undertaken, do the tuberculin skin test at six weeks and perhaps 12 weeks.

13.6.5 Another Member of the Family Is Being Treated for TB

The following steps apply if a family member with TB has completed treatment:

- Evaluate the family member before the newborn returns home.
- If the family is from a high prevalence group for TB, give the newborn a BCG vaccination, as per Victorian policy.

The following steps apply if the family member is on treatment:

- Prohibit the newborn from having contact with the TB patient for at least three months after the patient is culture negative.
- Give the newborn a BCG vaccination.

The following steps apply if the family member is infectious:

- Advise that the best course of action is for the child to have no contact with the infectious family member for at least three months after the patient is culture negative.
- If exposure is unavoidable or likely, give the child isoniazid until the index case is culture negative for three months.
- Alternatively, give the child a BCG vaccination before the family member returns to the household. The infected family member should not return until the newborn's tuberculin skin test is reactive.

13.6.6 Newborn Has Been Exposed to a Health Care Worker with Infectious TB

The following steps apply if the newborn, while in the nursery, has been exposed to a health care worker with infectious TB:

- Consider that infection, while rare under nursery conditions, can and does occur.
- Give isoniazid to the newborn for three months.
- After three months of isoniazid, repeat the tuberculin skin test and do a chest x-ray.
  (a) If the tuberculin reaction is negative and the chest x-ray is normal, discontinue treating with isoniazid.
  (b) If the tuberculin reaction is greater than 5 mm, investigate thoroughly for pulmonary and extra-pulmonary disease. If evidence of disease is present, then treat the newborn with multiple drug therapy.
  (c) If the tuberculin reaction is greater than 5 mm and there is no evidence of pulmonary and extra-pulmonary disease, continue treating with isoniazid to complete a six-month course.

13.7 Screening for TB during Pregnancy

Routine screening for TB during pregnancy is not necessary. Screening should be considered, however, for the following groups of pregnant women:

- Patients with symptoms suggestive of TB, indicating a tuberculin skin test and chest x-ray
- HIV infected patients (and other profoundly immunocompromised patients) — TST and chest x-ray are indicated
- Close contacts of infectious TB —TST, and chest x-ray if TST is significant
- Recent arrivals from high TB-prevalent countries who have not been screened previously for TB, indicating a tuberculin skin test (for which the reaction is likely to be significant) and chest x-ray if recent infection is suspected (to look for asymptomatic but radiological active pulmonary TB).

In asymptomatic pregnant women with a reactive tuberculin skin test, chest x-ray should be delayed until 12 weeks of gestation and 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.

13.8 Treatment of Latent TB Infection during Pregnancy

The risk of isoniazid hepatitis is higher for women than for men, and is higher in the post-partum period. Treatment of latent TB infection is usually withheld until after pregnancy, unless the patient has been recently infected (within the past two years), is HIV infected or has medical conditions that increase the risk for reactivation of inactive TB. For these women, treatment may be either given immediately or delayed until the second trimester.

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14. Airlines

14.1 Introduction

This chapter is particularly aimed at general practitioners, public health nurses and respiratory and infectious diseases specialists. The following two scenarios set the scene for the guidelines in this chapter.

Scenario 1: *A patient taking treatment for TB wishes to undertake air travel. How do you decide whether they pose a public health risk by doing so?*

Scenario 2: *A 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 notify their treating physician that they intend to travel overseas or they may make travel arrangements without consulting their physician. Approximately 80 per cent of new TB cases in Victoria are in foreign-born persons. Many of these cases are on short-term visas and are likely to want to travel during the six to 12 months during which they are on treatment. Issues of concern are (a) the risk of transmission of TB to other passengers and (b) the 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 these cases produced evidence of transmission of TB to susceptible passengers and flight crew (Driver et al., 1994; Kenyon et al., 1996; Wang, 2000) and some failed to demonstrate transmission (McFarland et al., 1993; Centers for Disease Control and Prevention, 1995; Miller, Valway and Onorato, 1996; Moore, Fleming and Sands, 1996; Parmet, 1999). The degree of risk of transmission of TB depends on the factors outlined in the following sections.

14.2.1 The Characteristics of the Index Case

Pulmonary and laryngeal TB are infectious, whereas extra-pulmonary 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 a chest x-ray. Culture-positive, smear-positive, cavitating pulmonary disease is highly infectious.

The following score for infectivity can be used to classify cases:

0 = Negligible infectivity	Extra-pulmonary disease
1 = Low infectivity	Smear- and culture-negative but active pulmonary disease
2 = Medium infectivity	Smear-negative, culture-positive pulmonary disease
3 = High infectivity	Smear-positive, culture-positive pulmonary disease or Culture-positive, cavitating pulmonary disease or Culture-positive laryngeal disease

An infectious case of active TB is defined as a case scoring 1 or more, and a non-infectious case is defined as one scoring 0. In general, a patient with pulmonary TB who complies with therapy and does not have drug-resistant disease should become non-infectious after two to three weeks of appropriate anti-tuberculous therapy.

14.2.2 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. A long flight, therefore, poses more risk than a short flight, and a flight of more than eight hours duration is associated with increased risk (World Health Organisation, 1998). There is also evidence that the risk of transmission is related to proximity to the infectious case (Kenyon et al., 1996).

14.2.3 Continuity of Treatment

It is undesirable to stop or interrupt treatment. Arrangements should also be made for overseas follow-up, if possible. A letter from the treating clinician outlining the person's clinical condition and required treatment is also helpful. The TB Program has a list of suitable medical contacts for many countries.

14.3 Recommendations

14.3.1 Infection Risk and Fitness to Travel

A patient with pulmonary or laryngeal TB should have at least two weeks of effective anti-tuberculous treatment and three consecutive negative sputum smears (performed on separate days) before being allowed to fly or placed in an enclosed environment conducive to the transmission of TB. A negative culture suggests the risk of transmission is greatly reduced.

Patients with extra-pulmonary TB carry a negligible risk of infectivity, but also should be commenced on effective anti-tuberculous treatment before travelling.

14.3.2 Continuation of Therapy

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 are important to ensure maximum compliance.

If a patient advises you that they intend to travel, notify the TB Program to ensure an adequate supply of medications and follow-up if necessary. The TB Program will work together with you to ensure maximum continuation of care.

14.4 What to Do if a Patient Informs You That They Intend to Travel

The decision to allow a patient on anti-tuberculous treatment to travel should be made on an individual basis, and should be discussed with the TB Program of the Department of Human Services. Where possible, alternative and private means of travel should be organised.

The patient should be encouraged to postpone travel plans until treatment is completed, if possible, or at least until one month of treatment has been successfully completed so antibiotic sensitivities are available and any adverse reactions to medications have been identified. The risk of infectivity can be assessed by the criteria set out in Section 14.2.1.

It is especially important that the TB Program be contacted to ensure continuation of therapy. If you have a patient on anti-tuberculous treatment who has indicated plans to travel overseas, then contact the Nurse Manager of the TB Program on (03) 9637 4110 to ensure appropriate medication supplies and follow-up.

14.5 Contact Tracing

The risk of transmission of *M. tuberculosis* on aircraft is low. Approximately two or three cases of active TB who have recently been on an airflight are notified to the Department of Human Services each year. The TB Program undertakes contact tracing to identify persons who might have been infected by the index case and who require medical evaluation, treatment and follow-up.

The barriers to successful contact tracing on airflights include the difficulty of obtaining passenger lists and/or contact details, a poor response rate from individuals contacted and the difficulty of interpreting a positive Mantoux screening test in contacts. Recent air travel (that is, since the onset of symptoms or within the previous six months) by cases of TB should be reported to the Department of Human Services on (03) 9637 4110.

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15. Migrant Screening for TB

15.1 Introduction

All non-citizens entering Australia on any type of residence visa other than a short term visitor's visa must meet the health requirements specified in the Migration Regulations. When visitors apply for an extension of their visa, they also must satisfy certain health requirements. The medical aspects of visa screening are handled by Health Assessment Services, a division of the Department of Immigration and Multicultural and Indigenous Affairs, which is based in Sydney. In Melbourne, Health Services Australia supervises activities on behalf of Health Assessment Services, particularly the screening of on-shore applicants for permanent residence, those applying for extension to other types of temporary residence and business visa, and overseas students applying for changes in their courses or extensions of their visas. Normally, students are screened in their country of residence, Health Assessment Services processes the results in Sydney, and the students are granted a visa for the expected duration of their proposed study program. Students are not further reviewed while they are in Australia, unless they change their study plans, their course, or the educational institution they attend.

Those intended migrants aged 16 years or more who are

- Applicants for permanent residence
- Applicants for various temporary residency categories
- Selected applicants, including visitors from certain high risk areas for three months or more
- Refugees, asylum seekers and those persons on temporary protection visas

must undergo a medical examination and have a chest x-ray which screens for TB and other conditions. Those aged 15 years or more who apply for permanent residency are also tested for HIV infection (all applicants) and hepatitis B infection (selected applicants). The same requirements apply to both offshore and on-shore applicants, irrespective of the country of application or origin. Those aged less than 16 years are given a medical examination, but chest x-ray and other screening tests are not normally required (apart from HIV serology for 15 years olds) unless clinical examination indicates otherwise.

Offshore applicants who have a chest x-ray indicating past or current TB infection are required to have further investigations in their country of application, including a repeat chest x-ray, consultant medical examinations, TB cultures and, where appropriate, a supervised course of treatment using a standard four-drug regimen. Applicants, including students, do not meet the health requirements until a Medical Officer of the Commonwealth is satisfied that active TB is not present.

Applicants with a history of TB or an abnormal chest x-ray must sign a Health Undertaking (TBU) before their visa is granted. This undertaking requires attendance at a State or Territory health facility as a condition of the visa so the applicant can be further assessed and treated if necessary. Onshore applicants who have a chest x-ray indicating past or current TB infection are likewise required to sign a TBU and are referred to a State or Territory health facility for management. Beyond the current provisions of the relevant State or Territory Health Act for constraining an individual with an active infectious disease, no legal mechanisms are available to enforce compliance with a TBU.

15.2 Management of TBUs

In Victoria, the Department of Human Services contracted the screening of all migrants and visitors on TBUs to Western Hospital, Footscray. Either Health Assessment Services or Health Services Australia makes direct referrals to the Migrant Screening Clinic. 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 is performed on those aged less than 35 years with an abnormal chest x-ray, on those aged less than 35 years with a normal chest x-ray if the person is a refugee or migrant from specified high risk countries (including Vietnam, the Philippines, China, Cambodia, India, Thailand and

countries from the Horn of Africa) and on other selected cases for whom it is appropriate to consider treatment of latent TB infection.

Those aged less than 35 years with a TST ≥ 15 mm are referred to an appropriate specialist clinic, preferably in their local area, for consideration of treatment of latent TB infection. A few individuals with smaller TST reactions are also referred at the discretion of the Migrant Screening Clinic.

Based on symptoms, examination, chest x-ray and selective TST, subjects are classified as having active TB, having inactive TB, having a non-TB abnormality or having no abnormality. Patients are referred for further management to the TB clinic at Western Hospital or elsewhere to an equivalent specialist clinic if:

- There is suggestion of active TB.
- There is extensive radiological abnormality of previous TB requiring further review.
- There is a case for considering treatment of latent TB infection.

If patients are thought to have non-TB-related medical conditions requiring ongoing management, then they are advised to seek further follow-up through their local medical practitioner or an appointment is made for them to see an appropriate specialist medical practitioner. Other patients who are regarded as normal are discharged from further review.

16. Contact Tracing

16.1 Introduction

TB 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 an integral part of any TB control program.

The aims of contact tracing are to identify the transmission of infection and to evaluate for the presence of infection and disease in the contacts of all notified cases of TB. TB remains highly emotive and stigmatised among some population sub-groups, who contribute the majority of annual TB cases in Australia. These sub-groups comprise those born overseas, from countries with a high prevalence of TB. It is opportune in contact tracing to target test for TB infection in the contacts of all notified cases of TB, infectious or non-infectious. Identified cases of TB infection can then be assessed for suitability for interventional measures and possible treatment of latent TB infection.

Conventional contact tracing procedures, as shown in recent studies, have their limitations in accurately identifying all cases of transmission of TB infection and disease. Improved techniques using DNA fingerprinting may lead to better detection of transmission.

16.2 Role of the TB Program, Department of Human Services

Successful contact tracing requires interpersonal, interviewing and counselling skills, patient assessment and a good clinical knowledge of TB. Since the inception of the State TB Control Campaign in the 1950s, the TB Program has had a team of public health nurses responsible for contact tracing. Review of notified cases and discussion of the intricacies/extent of contact tracing occurs weekly.

The TB Program provides a systematic approach to contact screening that ensures appropriate identification and investigation of contacts, to prevent or control the spread of infection. Central coordination of contact tracing is necessary to enable accurate surveillance data, that are important in identifying trends in the transmission of infection. The TB Program also has access to all relevant clinical details relating to the notified case, which ensures those at most risk of infection are investigated and effort is not wasted on screening those contacts at minimal risk.

16.2.1 Definitions

In contact investigations, the following definitions 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.
- 'Close contacts' are persons who have prolonged exposure to the index case, such as household members.
- 'Casual contacts' are individuals who have brief single encounters with, or minimal exposure to, the index case. The total time exposure is usually less than eight hours cumulatively.

16.2.2 Reasons for Contact Tracing

- To identify persons who have been exposed to the index case
- To identify persons who are infected (Recently infected persons are at greater risk of developing TB. They should be assessed medically for the presence of clinical TB and managed accordingly.)
- Where the index case is a child, to be thorough in identifying a source case of TB
- To identify environmental factors that may be contributing to the transmission of TB

16.2.3 Initiation of Contact Tracing

Once a suspected/confirmed case of infectious TB is notified, the initiation of contact investigation should be prompt. This urgency is based on the possibility that other infectious TB cases related to the notified case may exist. Initiation of contact investigation should not wait for positive culture if the history and other clinical findings are compatible with a diagnosis of TB.

16.2.4 Data collection

It is the duty of the public health nurse to collect all available information about the notified case from various sources (such as the reporting doctor, hospital records, the radiology facility and the laboratory) and collate them in a case/client record. The nurse will progress the data collection process by interviewing the 'patient' either in the hospital or at home.

16.2.5 Identification of Index Case Characteristics

Index case characteristics to be identified include:

- The clinical presentation of cough, whether it is productive/non-productive, and the duration of symptoms
- The site of disease
- The bacteriological results for sputum/bronchial washings, acid-fast bacilli smear/culture, nucleic acid amplification testing (PCR), bacteriological/histological examination of biopsy material, and, when available, results of molecular sub-typing or genetic 'fingerprinting' (RFLP)
- The radiological reports, the chest x-ray description of the extent of pulmonary disease (cavitary / non-cavitary), chest CT scans and other relevant imaging information.

16.2.6 Identification of Contact Characteristics

Contacts identified by the index case or self-identified can be placed in high risk or low risk categories.

High risk contact assessment factors are:

- Household contact
- Immunosuppression
- Age of less than 5 years
- Exposure within a confined area with inadequate air circulation.
- Prolonged duration of exposure to the index case (more than eight hours cumulatively).

16.2.7 Extent of Tracing

There is a need to set priorities and limits for contact tracing. Without a systematic approach, the investigative efforts will be wrongly directed on delivering services to those who do not have a demonstrated risk of TB infection or disease. In setting priorities for contact screening, the infectiousness of the index case is the most important determinant. Rapid contact tracing is clearly indicated when the TB case has a productive cough, there is x-ray evidence of cavitary disease, and the sputum smear for acid-fast bacilli is positive. In an extra-

Table 4: Index Case Assessment Factors

Infectivity	Disease	Smear	Culture
High	Cavitating pulmonary TB Pulmonary TB Tuberculous laryngitis	Positive (spontaneous sputum)	Positive
Medium	Pulmonary TB	Negative sputum smear Positive bronchial washings Positive induced sputum	Positive
Low	Pulmonary TB	Negative	Negative
Negligible	Extra-pulmonary TB		

pulmonary case with no respiratory symptoms, however, the likelihood of transmission would be negligible. Resist over-testing because it has undesirable consequences, such as the following:

- Widespread, unfocused testing reinforces the false assumption of an epidemic spread of TB—'If everyone is tested, there must be risk'.
- Widespread testing wastes valuable time and resources that are better used in identifying transmission among those at greatest risk
- Widespread testing will detect infection unrelated to the index case. It is then extremely difficult to convince positive tuberculin reactors that their infection is not the result of exposure to the case under investigation. As 'contacts', reactors may be offered treatment for latent TB infection, with its recognised adverse effects, when they would otherwise not be candidates for treatment as a result of age.

16.2.8 Who Should Be Screened?

- Close contacts and groups such as young children (5 years of age or younger) and the immunocompromised should be screened first.
- Where there is no evidence that transmission of infection has occurred, the contact survey need not extend beyond this group.
- Where there is evidence of infection in the close contacts (high risk group), the contact survey should be extended to include medium risk and low risk contacts.

16.3 Management of Contacts

16.3.1 Clinical Evaluation

- Assess contacts with symptoms of fever, cough and so on early, and refer them following TST and a chest x-ray.
- Carefully consider host factors such as diabetes, HIV or risk of HIV infection, and other immunosuppressive illnesses.

16.3.2 Tuberculin Skin Test

All contacts regardless of age are to have a TST test, with the exception of those who have a previously documented positive tuberculin reaction of 10 mm or greater, or those in special circumstances (such as residents of nursing homes, where in the elderly, the tuberculin skin test is of low predictive value).

16.3.3 Interpretation of Reaction and Subsequent Action

- Regardless of age, contacts who demonstrate a positive TST reaction of 10mm, with no evidence of prior Bacille Calmette-Guerin (BCG) vaccination, and who have a normal chest x-ray 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 latent TB infection.
- Regardless of age, contacts who demonstrate a positive TST reaction of 15mm, with evidence of previous BCG vaccination, and who have a normal chest x-ray should be referred to an appropriate physician or hospital for consideration of treatment for latent TB infection.
- All contacts with positive TST tests and abnormal chest x-rays must be referred to exclude active TB.
- For immunosuppressed persons and young children, a TST reaction >5 mm is significant, and these people should be referred for assessment.

16.3.4 Repeated Tuberculin Skin Tests

If the TST reaction is negative in the first round of testing, then the test should be repeated eight to 12 weeks later, unless at the time of the initial skin test eight to 12 weeks have already elapsed since last contact with the index case or since the index case commenced treatment (see Chapter 2, 'Tuberculin Testing').

16.3.5 Booster Phenomenon

Routine contact tracing does not necessarily look for the booster reaction. This is important where health care workers are serially tested to detect tuberculin conversion (see Chapter 2, 'Tuberculin Testing').

16.3.6 Chest X-Ray

- All TST positive contacts should have a chest x-ray.
- Contacts with a negative reaction should be considered on an individual basis, as per Chapter 2, 'Tuberculin Testing'.
- For chest x-rays and children, see Chapter 12, 'TB in Children and Adolescents'.
- All contacts with abnormal chest x-rays are referred for assessment.

16.3.7 Follow-Up of Contacts

- All contacts identified as being free of TB infection are discharged from follow-up.
- All contacts identified as being infected by the index case are followed up for a period of one and a half to two years if they are unable to tolerate or decline treatment for latent TB infection.

16.4 BCG Vaccination

BCG vaccination should be offered to contacts younger than 15 years of age, if they demonstrate a second negative TST test 'at break of contact', in the following circumstances:

- If the index case remains smear positive, and where the contact cannot be placed on isoniazid preventive therapy
- If the index case has multidrug-resistant TB (MDR-TB)
- If the contact belongs to a group at risk of repeated exposure to TB.

See Chapter 9, 'BCG Vaccination' for further information.

16.5 Special Categories

16.5.1 Neonates

This group is very susceptible to TB infection and progression to disease. Neonates must be 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 Chapter 13, 'TB and Pregnancy'.

16.5.2 Children

- All children aged 5 years old or younger who are close contacts of an acid-fast bacilli smear-positive case of pulmonary TB should be referred to the Royal Children's Hospital or a paediatric physician who is 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 with a positive TST test > 10 mm post-BCG vaccination or > 5 mm without a history of BCG vaccination should be referred to the Royal Children's Hospital or an appropriate paediatric physician.
- Chest x-rays will be performed at the time of appointment.

See Chapter 12, 'TB in Children and Adolescents' for further information.

16.5.3 Pregnancy

- A tuberculin skin test can be safely performed.
- A chest x-ray is withheld unless the woman is symptomatic, in which case referral is necessary.
- A chest x-ray is offered following delivery.

Refer to Chapter 13, 'TB and Pregnancy'.

16.5.4 Immunocompromised Contacts

Immunocompromised individuals, particularly those infected with HIV, may show a negative tuberculin response despite infection. They are to be referred to their treating physician irrespective of their TST reaction or the appearance of their chest x-ray.

16.5.5 Contacts of MDR-TB Cases

MDR-TB is not more virulent or more 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-TB disease are screened according to the same criteria as applies to all other contacts. Referral and follow-up are also carried out according to the same criteria, but the duration of follow-up should be longer (up to five years). More importantly, the

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

16.5.6 Large Scale Contact Screening

In settings such as schools, workplaces, nursing homes and prisons, conflicting interest groups sometimes dictate the limits of contact screening, and the TB Program has no choice but to accede to these demands. Whenever a TB case occurs in the above settings, the issues of privacy and confidentiality serve to hamper the identification of contacts. Recognising these difficulties, early communication with the management of the facility is vital to pre-empt unnecessary panic and anxiety about the 'contagiousness of TB'. The normal contact tracing procedures are observed, as in any other notified case of TB.

16.5.7 Contacts on Aircraft

The criteria set out by the World Health Organisation apply for contacts on aircraft (see Chapter 14, 'Airlines').

16.5.8 Contact Tracing in a Hospital Setting

The general principles of contact tracing still apply in a hospital setting. The length of time before the patient was placed in respiratory isolation must be determined, including time spent in the emergency or outpatient department, or in a general ward. Staff and patients sharing the same environment for more than eight hours with a case of infectious pulmonary TB, or anyone with an underlying immunosuppressed medical condition (such as HIV), must be treated as close contacts.

The TB Program will maintain close communication and consultation with the hospital infection control practitioner or its nominee in identifying all close contacts. 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. These patients should be advised that the TB Program will conduct appropriate screening investigations. The hospital should compile a list of discharged patients and forward it to the TB Program for follow-up.

16.5.9 Extra-Pulmonary TB

Contact tracing in cases of extra-pulmonary TB is undertaken for the following reasons:

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

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Appendix A: Abbreviations

AIDS	acquired immune deficiency syndrome
BCG	Bacille Calmette-Guerin
CD4	marker for specific T-lymphocyte subset with a central role in immune responses
CSIRO	Commonwealth Scientific and Industrial Research Organisation
DNA	deoxyribonucleic acid
DOT(S)	directly observed therapy (short course)
HRZE	isoniazid, rifampicin, pyrazinamide, ethambutol
HAART	highly active anti-retroviral treatment
HEPA	high efficiency particulate air
HIV	human immunodeficiency virus
IU	international unit
MDR-TB	multidrug-resistant tuberculosis
PPD	Purified Protein Derivative
TB	tuberculosis
TBU	Health (tuberculosis) Undertaking
TST	tuberculin skin test

Appendix B: Comment on Draft Guidelines

The draft guidelines were distributed for comment on 5 October 2001 in electronic and hard copy format. The draft document was also linked to the current guidelines on the Public Health website. The following organisations were invited to comment:

- Acute Health Division, Department of Human Services
- Australian Medical Association
- Australian Nursing Federation
- The departments of respiratory medicine at all Victorian metropolitan and major regional hospitals
- Dr Vicki Krause, Northern Territory Health Services and member of National Tuberculosis Advisory Council
- The infectious diseases units at all Victorian metropolitan and major regional hospitals
- Melbourne Infectious Diseases Group
- Mycobacteria Special Interest Group of the Australian Society for Microbiology
- Victorian Advisory Committee on Infection Control.

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