

# Tuberculosis (TB)

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## Introduction

*Mycobacterium tuberculosis* (MTB) is a bacterium which is estimated to currently infect over one third of the world's six billion people, causing over eight million new cases of disease annually.<sup>1</sup> Infection is much less common in populations with good access to health care and where overcrowded living conditions are uncommon. Most people infected with MTB will never realise it, as the immunity they develop contains the infection, but around 10-20% will at some stage become sick with active TB, a serious but curable disease.<sup>2</sup> Pulmonary TB is by far the most frequent presentation of disease and is the form primarily involved in the transmission of infection. Extra-pulmonary TB is rarely infectious and may affect the linings of the lungs or heart (causing pleural effusions or pericarditis), lymph nodes, bone and joints, genitourinary tract, brain (causing meningitis or space-occupying lesions), peritoneum or any other part of the body. All forms of active TB may present with systemic symptoms including fevers, weight loss, night sweats, and loss of appetite.

## Transmission of *Mycobacterium tuberculosis*

Infection is transmitted from one person to another by invisible droplets that are expelled into the air when coughing, sneezing, laughing or talking. These droplets can stay suspended in the air for a number of hours but are rapidly inactivated by sunlight. Those patients with the highest concentration of MTB in their lungs (smear-positive cases on sputum microscopy) are the most infectious.<sup>3</sup> Transmission is relatively inefficient, therefore the more time someone spends with an infectious case, the more chance they will become infected. The chance of infection will also be increased if the contact is close or occurs in rooms without good ventilation.<sup>4</sup>

## Epidemiology of TB in the Northern Territory

Each year there are between 30 and 60 new cases of active TB notified in the NT.<sup>5</sup> Approximately 60% of these occur in Aboriginal persons, 30% in migrants and 10% in the remainder of the community. Over the last 10 years, TB notification rates have averaged around 22 per 100 000 per annum in the NT compared to six per 100 000 in the wider Australian community in 1999.<sup>1</sup> The rate in NT Aboriginal and migrant communities has been approximately 40 per 100 000 per annum which is approximately 10 times the rate of four per 100 000 per year in the remainder of the NT population. About half of the NT cases occurred in people aged 15-44 years. The spectrum of disease in the NT is similar to that in other populations, with approximately 70% of new cases due to pulmonary TB, and the most common cause of extra-pulmonary disease being lymphadenitis.<sup>6</sup> Control of TB throughout the NT requires a

coordinated effort involving health staff from remote communities working in partnership with their patients and Department of Health and Community Services TB Control Units.

#### **Priorities for the control of TB in the Northern Territory**

- To rapidly identify and provide effective treatment and support to infectious cases with active TB, so the chance of transmission to others and the consequences of disease for the patient are reduced.
- To protect contacts of an infectious case with infection control measures instituted from the time active TB is first suspected until the case is no longer infectious.
- To identify and treat people with latent (asymptomatic) infection who are most at risk of developing active TB. At highest risk are recent contacts of infectious cases, especially young children and people who are immunosuppressed.
- To prevent severe disease in those at highest risk with BCG vaccination (i.e., very young children who are most susceptible to disseminated TB and tuberculous meningitis).
- To promote effective communication between urban and remote-area health staff and specialist TB units.

#### **Review**

Key questions for the control and management of TB within the CARPA manual use area:

- How can active TB be recognised quickly?
- What infection control measures can be instituted to prevent transmission once a suspected active case is identified?
- What treatment should be given to people with active TB?
- How can people with latent TB infection (LTBI) at highest risk of active disease be identified?
- How should people identified to have LTBI be managed?
- What are the indications for the appropriate use of BCG vaccination?
- How can effective communication between health staff and TB Control Units be facilitated?

#### **Prompt recognition of active TB**

##### **Symptoms and signs of active TB**

An important clue to the recognition and diagnosis of active TB is that it occurs with increased frequency in populations known to be at higher risk for transmission and/or progression of infection.<sup>7</sup> This includes Aboriginal people, migrants from high prevalence countries and people with chronic diseases such as HIV, diabetes, renal failure and malnutrition. Very few symptoms are specific to TB but persistence of symptoms is a very important feature of all forms of the disease. Pulmonary TB should be suspected if a cough lasts for longer than three weeks or is associated with blood-stained sputum. Unexplained weight loss, night sweats, fevers, tiredness and loss of appetite are also common features of pulmonary TB.

These non-specific symptoms may be the only feature of extra-pulmonary TB but symptoms and signs specific to the organs of involvement may also be present. These may include chest pain secondary to infection of the pleura

or pericardium, bone pain (the spine is most commonly involved), or abdominal swelling in the case of peritoneal disease. Persistent painless enlargement of lymph nodes, usually without systemic symptoms, is the most common presentation of tuberculous lymphadenitis and can also represent infection with non-tuberculous ('atypical') mycobacteria, especially in children.<sup>8</sup> Patients with tuberculous lymphadenitis may have been unsuccessfully treated with standard antibiotics previously. Alteration of conscious state or focal neurological signs in someone with fever or other systemic symptoms, especially in children, should prompt urgent in-hospital investigation that includes tests for tuberculous meningitis or tuberculous brain lesions.

## **Laboratory diagnosis of active TB**

### **Sputum collection**

A diagnosis of pulmonary TB can usually be made by collecting three early-morning sputum specimens and requesting laboratory examination by smear and culture for TB or 'AFBs' (acid fast bacilli).<sup>9</sup> Routine microscopy and culture should also be performed, including (in the Top End) selective tests for melioidosis.<sup>10,11</sup> Cytology should be ordered if lung cancer is part of the differential diagnosis (e.g., in smokers or older people with blood-stained sputum). It is desirable to collect these three specimens over three mornings in a row, as morning specimens give the best results.<sup>7</sup> However, it may be necessary to collect the first specimen immediately when the patient is first seen or to collect the other two on the same day if the person is highly mobile or likely to be difficult to follow up. Sputum specimens should be protected from light (as UV light kills MTB) by first sealing the containers in a plastic BioHazard bag and then placing the BioHazard bag into a brown paper bag. If the specimen cannot be transported to the laboratory within one hour of collection, then it should be refrigerated prior to and during transport.

Patients with pulmonary TB are infectious to other people and special care must be taken to prevent transmission of infection to contacts and health personnel (see below). Patients should be given a specimen container and asked to go outside into the fresh air away from other people to produce their sputum specimen. It may help the patient to cough if they have had a drink of water beforehand. A good sputum specimen is one which covers the bottom of the specimen container and contains very little saliva (it should stick to the bottom of the container when tipped upside down). Patients with suspected pulmonary TB who are unable to cough may be able to produce an induced sputum specimen with the help of a physiotherapist, or may require bronchoscopy for accurate diagnosis.<sup>2</sup>

### **Collection of gastric aspirates and tissue specimens**

Gastric aspirates, which contain sputum that has been swallowed overnight, may need to be collected to diagnose pulmonary TB in children and in adults who cannot produce sputum. The sensitivity of gastric aspirates for the diagnosis of pulmonary TB varies from 30-50% in those aged two to 12 years to up to 70% in infants less than two years of age.<sup>12</sup> As the best gastric aspirate specimens are those collected prior to waking, and the acid in the aspirate needs to be neutralised soon after collection, these are best collected in a hospital environment.<sup>13</sup> Patients with extra-pulmonary TB will usually require a fine needle aspirate or biopsy for microscopic examination and culture to confirm the diagnosis. Specimens collected in this way should be sent to an appropriate laboratory without delay in a

small amount of normal saline. Biopsy specimens must not go into formalin as this will kill any MTB organisms present.

#### **Role of tuberculin skin testing (Mantoux) in diagnosis of active TB**

The Mantoux test is not a good test to diagnose active TB<sup>14</sup>, especially in adults. Negative Mantoux tests will be observed in approximately 10–25% of patients with active TB<sup>15,16</sup>, therefore the Mantoux test cannot be used to eliminate the possibility of active TB.<sup>2</sup> Because active TB is more frequent in risk groups with a high prevalence of latent TB infection, Mantoux tests will often be positive even when disease is not present – i.e. the predictive value of a positive test is very low.<sup>17</sup> Therefore, in adults, the focus of investigation should be to obtain relevant sputum and tissue specimens for microscopy and culture as this decision will not be influenced either way by a Mantoux result. A positive Mantoux test in association with a compatible clinical picture is more suggestive of disease in children where the likelihood of false-negative reactions is approximately 10% and the background prevalence of infection is expected to be low.<sup>18</sup> Its use in this context should be discussed with an expert in the management of TB.

#### **HIV testing**

The highest rate of reactivation of latent TB infection occurs in patients with human immunodeficiency virus (HIV) infection – roughly 10% per year as opposed to 10% per lifetime if HIV-negative.<sup>19</sup> Active TB may present early on in the course of HIV infection, before patients become significantly immunosuppressed.<sup>20</sup> Because treatment is now available that will significantly improve the prognosis of patients with HIV<sup>21</sup>, all patients with active TB should be counselled and advised to undergo HIV testing. It is hoped that this strategy will identify people earlier in the course of their HIV infection at a time when treatment may provide the most long-term benefit.

#### **Infection control measures**

##### **Prevention of airborne transmission**

The risk of transmission of MTB to others can be minimised by instituting sensible infection control procedures once a case of suspected pulmonary TB has been recognised. Because MTB is spread by airborne droplet nuclei, transmission to contacts may be reduced by asking the patient to cover their mouth and nose with a handful of tissues or a handkerchief when coughing and sneezing.<sup>22</sup> Facemasks designed to filter fine particles have also been suggested for patients and health staff to decrease expulsion of bacilli and inhalation of droplet nuclei. A recommended particulate filter mask is one which provides face-seal leakage of less than 10% and that has greater than 95% efficiency in filtering 0.3 micron particles (e.g., 'duck-bill' masks).<sup>23</sup>

##### **Travel and hospitalisation of patients with suspected active TB**

People with suspected active TB should only travel by air on commercial aircraft if known to be smear-negative on three separate sputum smears.<sup>24</sup> Patients who are smear-positive or whose sputum smears have not been examined should wear a mask during transport and only travel by air with an air medical service, preferably without other patients on board. Road travel should be undertaken with masks on and windows down to promote

maximum ventilation. Suspected TB cases should be housed in hospital in single rooms with negative pressure ventilation and respiratory isolation precautions until three separate early morning sputum smears are negative.

## **Treatment of active TB**

### **Drug therapy**

Treatment of TB typically requires at least six months of multi-drug therapy and is extremely effective for most forms of disease.<sup>25</sup> Some forms of extrapulmonary disease may require longer therapy up to and in excess of 12 months on occasions (e.g., disseminated TB, bone and joint disease and cerebral tuberculomas). Treatment may need to be started in hospital if infection control measures are required for smear-positive patients, but may sometimes be started as an outpatient if the risk of transmission to others is judged to be very low. Patients who were smear-positive on sputum microscopy will usually be non-infectious after two weeks of effective treatment.<sup>26</sup> Patients with more advanced cavitary disease may take longer, sometimes months, to become smear-negative.

Four anti-TB drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) should be given initially to rapidly decrease the burden of tuberculous bacilli and to cover the possibility of drug resistance. Pyrazinamide may be poorly tolerated by elderly people and ethambutol should not be used in people who might have difficulty in reporting visual loss, e.g., those with large cataracts or children under six years of age. Pyrazinamide and ethambutol can usually be ceased after two months if susceptibility tests confirm no drug resistance. Rifampicin and isoniazid are continued for the duration of therapy. Different combinations may be required depending on whether the patient's MTB isolate is resistant to first line drugs or if side effects occur on standard therapy. Pyridoxine (vitamin B6) is given at the same time to minimise the risk of isoniazid-induced peripheral neuropathy.<sup>19</sup> Drug dosages can be found in standard treatment guidelines<sup>27,28</sup> and may require adjustment during therapy for changes in body weight. Monthly clinical monitoring for side effects is necessary for all patients and monthly liver function tests will be necessary for people at increased risk of liver toxicity.<sup>27</sup>

### **Helping patients complete their treatment**

Completing a full course of treatment for active TB or latent TB infection can be difficult because of the complexity of multi-drug regimens and the length of therapy. However, it is extremely important that the patient is supported and able to take all of their prescribed therapy, as interruptions or early cessation of the treatment regimen can lead to the serious problem of emergence of drug resistance, which can make re-treatment more difficult in both the index case and any secondary cases in contacts. Patients may be more motivated if they and their families have received education about the disease and its treatment in their primary language.<sup>29</sup> This should be done with the help of visual aids and through an interpreter whenever one is available. It should be explained that it will usually be possible to simplify the drug regimen after two months of therapy. Providing feedback to patients during therapy may also help to enhance adherence to the drug regimen. Showing patients how chest X-ray changes improve with treatment can be very useful in this regard.

Patients should be warned that their urine will turn a pink to orange colour while taking rifampicin but that this is not at all harmful, in fact

it can be a good sign that the drug is being absorbed and doing its work. It is extremely important that patients are told to look out for common (e.g., skin itch, difficulty sleeping or concentrating) and potentially serious side effects. The latter includes symptoms of liver toxicity such as nausea; loss of appetite; abdominal pain and tenderness; darkening of the urine (jaundice). Pyrazinamide may also cause gout and ethambutol can result in loss of visual acuity. Patients should be advised not to drink alcohol while on therapy as it may enhance the risk of liver toxicity.<sup>30</sup> Nothing is more important than telling all patients on TB therapy of any kind to stop their medication and seek help immediately if they develop any new symptoms, as these may represent drug toxicity.

The most effective way of ensuring that a patient can adhere to their treatment regimen is to administer their therapy under direct supervision.<sup>31</sup> This is called Directly Observed Therapy (DOT).<sup>32</sup> DOT works best when the patient has easy access to their medication either by having the medicine brought out to them or being able to access their medicine from a clinic without having to wait. To facilitate DOT, most anti-TB drug regimens can be given two to three times weekly at doses higher than the usual daily dose. DOT is given three times weekly in the NT. Any missed doses should be added to the end of the treatment regimen so that all the intended doses get taken, even though this means extending treatment. Management of patients who have a prolonged break from therapy will need to take into consideration issues of possible disease relapse or drug resistance and should be done with the consultation of regional TB Control Units.

### **Diagnosis of latent TB infection (LTBI) in people at high risk**

Identification of people with LTBI is an essential component of TB control programs in developed countries. Treatment of LTBI will substantially reduce an individual's risk of developing active TB and also potentially decrease transmission within a community.<sup>19</sup> The most efficient use of this control strategy is to target individuals at highest risk of being infected or developing disease. This includes recent contacts of infectious cases (whose risk of infection may be as high as 50%<sup>3</sup>), people with LTBI who have reduced immunity to MTB (e.g., because of immunosuppressive drugs like high-dose or prolonged steroids; or chronic diseases including HIV, diabetes, renal failure and malnourishment) and people with fibrotic chest X-ray changes of TB.<sup>33</sup> Children are at particularly high risk.

### **Contact tracing**

Contact tracing of people exposed to an infectious (index) case of TB is vitally important to prevent more people getting sick and to interrupt transmission within a community. To be effective, contact tracing necessarily involves a lot of time and must begin as soon as possible after a presumptive diagnosis of active TB has been made. The efficiency of contact tracing will be enhanced when local health staff work together in partnership with the index case, their family (with the index case's consent) and the regional TB Control Unit whose responsibility it is to coordinate the process. The risk of transmission to contacts will be highest when the index case is smear-positive for AFBs on sputum smear and when the degree of contact is close.<sup>7</sup> Household contacts and school or workplace contacts who work alongside the index case are the highest priorities in contact tracing. If evidence of transmission is found within these groups, then lower-risk contacts will also need to be followed up.

Contact tracing should begin by providing the index case with an understanding of the contact tracing process and educating them about the benefits of early diagnosis and treatment for their friends and families. If the patient is agreeable, this is often best explained in the company of their family. Contact lists should be drawn up of all contacts going back at least three months (longer if the patient's symptoms began before this), identifying each according to their level of exposure. The highest priority will be given to close contacts (as above), especially young children and adolescents. It is extremely important to screen contacts for symptoms and signs of active TB as these may have developed recently. Details of prior Mantoux tests, treatment of latent or active TB and chest X-ray results should be checked for each contact with the regional TB Control Unit. Further decision making with regard to Mantoux testing, chest X-ray, and treatment of latent or active TB (below) needs to be made in consultation with the regional TB Control Unit.

Contact tracing for lower-risk cases of active TB (including smear-negative pulmonary TB and extra-pulmonary disease) is also important, as friends and family are likely to have shared similar exposure to the person from whom their friend or relative has acquired their infection. This will also be true for children who are discovered on school screening to have a positive Mantoux test without symptoms of active TB, as they are likely to have been infected with TB relatively recently and other members of the family may also be at risk.

### **Mantoux testing**

The Mantoux method of tuberculin skin testing remains the most reliable and widely validated means of assessing whether an individual has been infected with MTB. In vitro assays of the cellular immune response to tuberculous proteins (such as the QuantiFERON™ test) currently offer few advantages over Mantoux testing, as false-positive results occur in BCG-vaccinated subjects<sup>34</sup> and there has been far less experience with their use. This situation may change as assays are developed that measure the immune response to MTB-specific PPD subunit proteins that are not present in BCG vaccine strains of *M. bovis*.<sup>35</sup>

Assessment of an individual's cutaneous reaction to tuberculin must take account of the size of the reaction, the predictive value of the test based on possible causes of false-negative and false-positive reactions and the risk of development of active TB. Readers are referred to the most recent Centre for Disease Control Guidelines for the Control of TB in the Northern Territory for the interpretation of Mantoux tests. Note that repeat testing of contacts 10 weeks after their last exposure to an infective case is often required as it can take that long for a person to develop an immune response to MTB that is detectable by Mantoux testing.<sup>16</sup>

Because of the difficulty in interpretation of Mantoux tests in people at low risk for TB, there has been a trend towards targeting testing toward people at higher risk who will benefit the most from treatment of LTBI.<sup>19</sup> This includes contacts of a case of active TB (as defined above) but also people at increased risk of progression of LTBI to active TB. The latter group includes people with chest X-ray changes that could be consistent with previous TB infection, recent migrants (assumed to have been exposed up to the time of departure) and patients who are immunosuppressed because of disease (e.g., HIV, diabetes, renal failure, malnutrition) or drugs (e.g., oral steroid therapy). A baseline Mantoux test should also be done for staff who will be working in settings with evidence of increased TB

transmission (e.g., Aboriginal health centres, drug and alcohol rehabilitation centres, prisons and hospitals).

Mantoux tests should not be done in people with prior Mantoux results of 15 mm or greater or previous known TB, therefore an inquiry should be made to the regional TB Control Unit as to a person's prior Mantoux and TB history before testing.

## **Treatment of latent TB infection**

### **Benefits of treatment**

With few exceptions, in people targeted for Mantoux testing because of an increased risk of infection or disease the decision to test can be regarded as the decision to treat.<sup>19</sup> This statement reflects the view that the benefits of treating LTBI will outweigh the risks in patients of all ages if they are selected on the basis of being in an at-risk group without significant contra-indications to treatment.<sup>36</sup> Recent evidence indicates that the risks of isoniazid toxicity, particularly liver toxicity, are lower than previously assumed, especially if treatment is monitored appropriately.<sup>37-40</sup> Isoniazid alone can be expected to reduce an individual's risk of developing active TB by between 65-75%, depending on the length of therapy.<sup>41</sup> With good adherence to therapy (>80% of doses taken), this benefit may rise to 69-93%.<sup>33</sup>

### **Drug regimens used for treatment**

The standard six month isoniazid recommendation (either daily or 2-3 times weekly) for the treatment of LTBI has recently been revised and updated.<sup>19</sup> This followed a review<sup>42</sup> of older studies demonstrating longer regimens to be more efficacious<sup>33,43,44</sup> and newer studies showing decreased liver toxicity in patients on isoniazid who were appropriately monitored.<sup>38</sup> The American Thoracic Society (ATS) and US Centers for Disease Control (CDC) and Prevention have firmly recommended nine months of isoniazid as preferred therapy for the treatment of LTBI in children under 18 years of age, persons with HIV infection and persons with chest X-ray changes consistent with prior TB. Six month regimens of isoniazid are considered an acceptable alternative for other groups of adults where the risks of active TB and advantages of longer therapy may be lower, however, nine months is still preferred. Daily isoniazid can be provided to adults in dosette boxes that are filled weekly if they are not likely to experience problems with adherence to therapy. In children <15 years and adults who may have difficulty with adherence to the daily regimen, isoniazid should only be given as directly observed therapy 2-3 times weekly.

A number of new regimens for the treatment of LTBI have recently been recommended for HIV-positive and HIV-negative adults on the basis of clinical studies in HIV-positive populations.<sup>45-47</sup> In general, these regimens have been shown to be as effective as isoniazid with the advantage of being significantly shorter. They may be of use where adherence to therapy is expected to be difficult or where limited time or resources make short-course therapy more feasible than with longer regimens. An example of such a regimen is rifampicin plus pyrazinamide given by DOT twice weekly for two months. The higher costs of the drugs in these regimens may be offset by decreased administration costs and opportunity costs related to a decrease in active TB rates. However, there have been recent reports of toxicity (including deaths) associated with rifampicin plus pyrazinamide therapy.<sup>48</sup> This has led to a revision of the recent ATS and US CDC guidelines with an

emphasis on restricted patient selection and frequent clinical and laboratory monitoring.<sup>49</sup>

### **Monitoring of treatment**

Careful monitoring of patients taking treatment for LTBI should consist of regular monthly clinical reviews and instructions to stop treatment and report immediately any symptoms that may be due to drug toxicity. This is especially important for symptoms of possible liver toxicity such as nausea, loss of appetite, abdominal tenderness and jaundice. Liver function tests should be done at baseline and every month in patients at increased risk of liver toxicity, including all patients over 35 years, those with increased risk of chronic hepatitis (e.g. due to hepatitis B, C or alcohol) and special subgroups such as HIV-positive and pregnant women. Similarly, LFTs and full blood examinations need to be done fortnightly in all patients taking regimens containing rifampicin and pyrazinamide.

### **Indications for BCG vaccination**

Recommendations regarding the use of BCG vaccination vary from country to country and within different population groups.<sup>50,51</sup> Two recent meta-analyses have concluded that the protective efficacy of BCG vaccination for preventing serious manifestations of TB, such as meningitis in children, is high (>80%).<sup>52,53</sup> However, the efficacy of BCG vaccination in preventing pulmonary TB in adolescents and adults remains uncertain despite years of experience with its use. Furthermore, BCG vaccination in low-risk populations makes assessment of tuberculin skin tests difficult due to the high incidence of false-positive reactions. BCG vaccination is therefore not currently recommended for Australians older than five years.

It is generally accepted that selective use of BCG vaccination is warranted for vulnerable young children from high-risk populations.<sup>54</sup> It is recommended that Aboriginal babies be vaccinated at birth in the NT. Children under five years who will be living overseas in countries with high TB prevalence or in Aboriginal communities for longer than three months should also be vaccinated with BCG. BCG vaccine may cause local reactions in children previously infected with TB; therefore should be preceded by Mantoux testing in children over six months of age or in infants less than six months of age with a history of exposure to an index case with active TB. There are other contraindications and side effects related to the use of BCG vaccination<sup>54</sup>, therefore it should only be given by people skilled in its administration.

### **Communication between health staff and TB control units**

TB Control Units are divisions of the Centre for Disease Control, which in turn is governed by the NT Department of Health and Community Services. The central TB Control Unit is located in Darwin and there are regional TB Control Units located in Nhulunbuy, Katherine and Alice Springs. These units maintain primary responsibility for coordinating aspects of TB control in Northern Territory including:

- Recording notification of all cases of active TB and results of all Mantoux tests on a database accessible by remote area health staff.
- Production of evidence-based standard treatment guidelines (last edition Guidelines for the Control of TB in the Northern Territory, 1997, under revision 2002).

- Coordination and help with contact tracing.
- Provision of resources such as educational material, standard data collection, treatment and information forms, tuberculin (PPD) for Mantoux testing, BCG vaccine and anti-TB medications (free for all patients who require it).
- School screening and screening of other high-risk groups (such as migrants and prisoners).
- Providing advice to health staff throughout the NT on all aspects of control and management of TB at all levels from public health through to individual patient management.
- Outpatient TB clinics are held at each of the CDC centres. Bookings can be made on the phone numbers below.

Out-of-hours advice for information about TB can be obtained through the medical registrar on call at Royal Darwin Hospital and from Darwin CDC on-call personnel who may be contacted through the Royal Darwin Hospital switchboard (phone (08) 8922 8888).

Contact details for each of the TB Control Units are as follows:

#### **Darwin region**

Centre for Disease Control  
 PO Box 40596  
 Casuarina NT 0811  
 Phone: (08) 8922 8804 switch, (08) 8922 8522 direct  
 Fax: (08) 8922 8310

#### **Central and Barkly regions**

Centre for Disease Control  
 PO Box 721  
 Alice Springs NT 0871  
 Phone: (08) 8951 7548 direct  
 Fax: (08) 8951 7900

#### **East Arnhem region**

Centre for Disease Control  
 PO Box 421  
 Nhulunbuy NT 0881  
 Phone: (08) 8987 0282 switch, (08) 8987 0359 direct  
 Fax: (08) 8987 0355

#### **Tennant Creek and Barkly region**

Centre for Disease Control  
 PO Box 346  
 Tennant Creek NT 0861  
 Phone: (08) 8962 4399, (08) 8962 4259, (08) 8962 4420

#### **References**

1. World Health Organisation. Global Tuberculosis Control. WHO Report 2001. Geneva, Switzerland: World Health Organisation, WHO/CDS/TB/2001.287; 2001.
2. American Thoracic Society/Centers for Disease Control. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. Am J Respir Crit Care Med 2000; 161(4Pt1):1376-95.

3. Styblo K. Recent advances in epidemiological research in tuberculosis. *Adv Tuberc Res* 1980; 20:1-63.
4. Houk VH, Kent DC, Baker JH, Sorensen K, Hanzel GD. The Byrd study. In-depth analysis of a micro-outbreak of tuberculosis in a closed environment. *Arch Environ Health* 1968; 16(1):4-6.
5. Centre for Disease Control. Cumulative data from THS Annual Reports & NT Disease Control Bulletins. Darwin, NT: Centre for Disease Control and Territory Health Services, 2000.
6. Carnie J, Christensen A, Eyeson-Annan M, Gill J, Konstantinos A, Krause V et al. Tuberculosis notifications in Australia, 1998. *Commun Dis Intell* 2001; 25(1):1-8.
7. Haas DW, des Prez RM. *Mycobacterium tuberculosis*. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. 4th ed. New York: Churchill Livingstone; 1995: 2213-43.
8. Spyridis P, Maltezos HC, Hantzakos A, Scondras C, Kafetzis DA. Mycobacterial cervical lymphadenitis in children: clinical and laboratory factors of importance for differential diagnosis. *Scand J Infect Dis* 2001; 33(5):362-6.
9. Laszlo A. Technical guide: Sputum examination for tuberculosis by direct microscopy in low income countries. 5th ed. Paris, France: International Union Against Tuberculosis and Lung Disease, 2000.
10. Currie BJ, Fisher DA, Howard DM, Burrow JN, Lo D, Selva-Nayagam S et al. Endemic melioidosis in tropical northern Australia: a 10-year prospective study and review of the literature. *Clin Infect Dis* 2000; 31(4):981-6.
11. Currie BJ, Fisher DA, Howard DM, Burrow JN, Selvanayagam S, Snelling PL et al. The epidemiology of melioidosis in Australia and Papua New Guinea. *Acta Trop* 2000; 74(2-3):121-7.
12. Kahn EA, Starke JR. Diagnosis of tuberculosis in children: increased need for better methods. *Emerg Infect Dis* 1995; 1(4):115-23.
13. Pomputius WF, III, Rost J, Dennehy PH, Carter EJ. Standardization of gastric aspirate technique improves yield in the diagnosis of tuberculosis in children. *Pediatr Infect Dis J* 1997; 16(2):222-6.
14. Street AC. Tuberculosis. In: Yung AP, McDonald MI, Spelman DW, Street AC, Johnson PDR, editors. *Infectious Diseases a Clinical Approach*. 1st ed. Melbourne: Melbourne University Press, 2001: 274-85.
15. Steiner P, Rao M, Victoria MS, Jabbar H, Steiner M. Persistently negative tuberculin reactions: their presence among children with culture positive for *Mycobacterium tuberculosis* (tuberculin-negative tuberculosis). *Am J Dis Child* 1980; 134(8):747-50.
16. Huebner RE, Schein MF, Bass JB, Jr. The tuberculin skin test. *Clin Infect Dis* 1993; 17(6):968-75.
17. Canadian Lung Association/Canadian Thoracic Society. Diagnosis of Tuberculosis Infection and Disease. In: Long R, editor. *Canadian Tuberculosis Standards*. 5 ed. Government of Canada, 2000: 45-65.
18. Starke JR. Diagnosis of tuberculosis in children. *Pediatr Infect Dis J* 2000; 19(11):1095-6.
19. American Thoracic Society/Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. This statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999. *Am J Respir Crit Care Med* 2000; 161(4 Pt 2):S221-S247.
20. Castro KG. Tuberculosis as an opportunistic disease in persons infected with human immunodeficiency virus. *Clin Infect Dis* 1995; 21(Suppl1):S66-S71.
21. Andrews L, Friedland G. Progress in HIV therapeutics and the challenges of adherence to antiretroviral therapy. *Infect Dis Clin North Am* 2000; 14(4):901-28.
22. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep* 1994; 43(RR-13):1-132.
23. Curran E, Ahmed S. Do health care workers need to wear masks when caring for patients with pulmonary tuberculosis? *Commun Dis Public Health* 2000; 3(4):240-3.
24. World Health Organisation. Tuberculosis and air travel: Guidelines for prevention and control. Geneva, Switzerland: World Health Organisation, WHO/TB/98.256; 1998.
25. Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity, and acceptability. The report of final results. *Ann Intern Med* 1990; 112(6):397-406.
26. Rouillon A, Perdrizet S, Parrot R. Transmission of tubercle bacilli: The effects of chemotherapy. *Tubercle* 1976; 57(4):275-99.
27. Centre for Disease Control. Guidelines for the control of tuberculosis in the Northern Territory. Darwin: Territory Health Services, 1997.
28. Antibiotic Guidelines Writing Group. Mycobacterial infections. Therapeutic guidelines: Antibiotic. 11th ed. Melbourne: Therapeutic Guidelines Limited, 2000: 101-6.

29. Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of pulmonary tuberculosis: Consensus Statement of the Public Health Tuberculosis Guidelines Panel. *JAMA* 1998; 279(12):943-8.
30. Gilroy SA, Rogers MA, Blair DC. Treatment of latent tuberculosis infection in patients aged greater than or equal to 35 years. *Clin Infect Dis* 2000; 31(3):826-9.
31. Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney GB et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med* 1994; 330(17):1179-84.
32. World Health Organisation. What is DOTS? A guide to understanding the WHO recommended TB control strategy known as DOTS. Geneva, Switzerland: World Health Organisation, WHO/CDS/CPC/TB/99.270, 1999.
33. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull. WHO* 1982; 60(4):555-64.
34. Johnson PD, Stuart RL, Grayson ML, Olden D, Clancy A, Ravn P et al. Tuberculin-purified protein derivative-, MPT-64-, and ESAT-6-stimulated gamma interferon responses in medical students before and after *Mycobacterium bovis* BCG vaccination and in patients with tuberculosis. *Clin Diagn Lab Immunol* 1999; 6(6):934-7.
35. Lalvani A, Pathan AA, Durkan H, Wilkinson KA, Whelan A, Deeks JJ et al. Enhanced contact tracing and spatial tracking of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells. *Lancet* 2001; 357(9273):2017-21.
36. Horsburgh CR, Jr., Feldman S, Ridzon R. Practice guidelines for the treatment of tuberculosis. *Clin Infect Dis* 2000; 31(3):633-9.
37. Millard PS, Wilcosky TC, Reade-Christopher SJ, Weber DJ. Isoniazid-related fatal hepatitis. *West J Med* 1996; 164(6):486-91.
38. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999; 281(11):1014-8.
39. Salpeter SR. Fatal isoniazid-induced hepatitis. Its risk during chemoprophylaxis. *West J Med* 1993; 159(5):560-4.
40. Salpeter SR, Sanders GD, Salpeter EE, Owens DK. Monitored isoniazid prophylaxis for low-risk tuberculin reactors older than 35 years of age: a risk-benefit and cost-effectiveness analysis. *Ann Intern Med* 1997; 127(12):1051-61.
41. Smeja MJ, Marchetti CA, Cook DJ, Smail FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst Rev* 2000; (2):CD001363.
42. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis* 1999; 3(10):847-50.
43. Comstock GW, Ferebee SH, Hammes LM. A controlled trial of community-wide isoniazid prophylaxis in Alaska. *Am Rev Respir Dis* 1967; 95(6):935-43.
44. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc* 1970; 26:28-106.
45. Halsey NA, Coberly JS, Desormeaux J, Losikoff P, Atkinson J, Moulton LH et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet* 1998; 351(9105):786-92.
46. Mwinga A, Hosp M, Godfrey-Faussett P, Quigley M, Mwaba P, Mugala BN et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS* 1998; 12(18):2447-57.
47. Gordin F, Chaisson RE, Matts JP, Miller C, de Lourdes GM, Hafner R et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beinr Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. *JAMA* 2000; 283(11):1445-50.
48. Centers for Disease Control and Prevention. Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection—New York and Georgia, 2000. *MMWR Morb Mortal Wkly Rep* 2001; 50(15):289-91.
49. Centers for Disease Control and Prevention. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society / CDC recommendations — United States, 2001. *MMWR Morb Mortal Wkly Rep* 2001; 50(34):733-5.
50. Centers for Disease Control and Prevention. The role of BCG vaccine in the prevention and control of tuberculosis in the United States. A joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 1996; 45(RR-4):1-18.
51. Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. *Thorax* 2000; 55(11):887-901.

52. Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *Int J Epidemiol* 1993; 22(6):1154-8.
53. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA* 1994; 271(9):698-702.
54. Australian Technical Advisory Group on Immunisation. Tuberculosis. The Australian immunisation handbook. 7 ed. Commonwealth of Australia, 2000: 220-6.