THE NORTHERN HOSPITAL

TUBERCULOSIS

Right panel: "The Sick Child", Lithographic study, 1896, Edvard Munch.

Left panel: "The Sick Child" oil on canvas, 1896, Edvard Munch, National Gallery, Oslo, Norway.

"...I leave no one to regret me much: I have only a father; and he is lately married, and will not miss me. By dying young, I shall escape great sufferings. I had not qualities or talents to make my way very well in the world: I should have been continually at fault."
"But where are you going to, Helen? Can you see? Do you know?"
"I believe; I have faith. I am going to God."
"Where is God? What is God?"
"My Maker and yours, who will never destroy what He created. I rely implicitly on his power, and confide wholly in His goodness: I count the hours till that eventful one arrives which shall restore me to Him, reveal Him to me."
"You are sure, then, Helen, that there is such a place as heaven: and that our souls can get to it when we die?"
"I am sure there is a future state; I believe God is good; I can resign my immortal part to him without misgiving. God is my father; God is my friend; I love him; I believe He loves me."
"And shall I see you again Helen when I die?"
"You will come to the same region of happiness: be received by the same mighty universal Parent no doubt dear Jane."
Again I questioned; but this time only in thought.
"Where is that region? Does it exist?" And I clasped my arms closer round Helen; she seemed dearer to me than ever; I felt as if I could not let her go; I lay with my face hidden on her neck. Presently she said in the sweetest tone-
"How comfortable I am! The last fit of coughing has tired me a little; I feel as if I could sleep; but don't leave me Jane; I like to have you near me."

"I'll stay with you, dear Helen: no one shall take me away."
"Are you warm darling?"
"Yes"
"Goodnight Jane."
"Goodnight Helen."
She kissed me, and I her and we both soon slumbered. When I awoke it was day: an unusual movement roused me; I looked up; I was in somebody's arms; the nurse held me; she was carrying me through the passage back to the dormitory. I was not reprimanded for leaving my bed; people had something else to think about; no explanation was afforded to my many questions; but a day or two afterwards I learned that Miss Temple on returning to her own room at dawn, had found me laid in a little crib; my face against Helen Burns's shoulder, my arms round her neck. I was asleep, and Helen was…dead.
Her grave is in Brocklebridge Churchyard: for fifteen years after her death it was only covered with a grassy mound; but now a gray marble tablet marks the spot, inscribed with her name, and the word "Resurgam."

"Jayne Eyre", Charlotte Bronte, 1847.

Throughout the 19th and early 20th century a "Grim Reaper" stepped out from the shadows to wreak havoc on the rapidly industrializing nations of the west. It had always been present but standing constantly and silently in the background taking a relatively small but steady toll over the millennia of recorded human history and probably for much longer than that. This reaper was known traditionally as phthisis but during the course of the Nineteenth century as it began to take a fearful toll it became known as "consumption". Like a cancer it would literally consume those afflicted with it, painfully, miserably and inexorably. Most dreadfully of all it would take the young and seemingly most healthy. The course of the disease, in contrast to the explosive "pestilences" of previous ages that would seemingly appear from nowhere only to disappear just as suddenly, was slow, relentless and ever present. It progressed inexorably as the 19th century wore on into the early 20th century with no end to it in sight. By the dawn of the 20th century it had become the number one killer of children and young people within the newly industrialized nations. It was the single greatest check to the seemingly boundless religious and scientific optimism of those times. The scientific hope of man's unlimited capacity for progress at the dawn of the 20th century was severely shaken by the medical profession's complete impotence to treat it. So great had become the fear of the pestilence that a new term evolved for it at this time, "The White Death", as if to echo the memory of it's more infamous chromatic antithesis of the mid fourteenth century. It was "white" not only because of the progressive anaemia it seemed to induce but also because of it's preference for the young and innocent. Because it affected so many of the young and talented throughout the 19th century a rich artistic and literary legacy has been left to us of this reaper.

Perhaps the most poignant vision of the white death that has come down to us is Edvard Munch's, "The Sick Girl" painted in 1896. Munch lost his eldest sister Sophie to the white death at the age of fourteen. Following her death he was to be haunted and tortured by the memory of her suffering for the rest of his life. In the picture the sick girl appears to stare out through the window as if glimpsing a vision of the next world she looks forward to as the only means of relieving her suffering, seemingly

oblivious to her weeping companion who lowers her face unable to look into the staring eyes of her dying friend.

In the literary genre Charlotte Bronte's heart rending experiences of the loss of her two older sisters aged just ten and twelve years are echoed in her immortal Jane Eyre. The white death had swept through the boarding school where Charlotte and her three sisters were staying. The deaths of her two older sisters were a life altering nightmare from which she never recovered. Her mother had also died of consumption as she herself would do so at the age of thirty eight.

Robert Koch made one of medicine's most brilliant discoveries when in 1882 he identified the cause of the White Death, the tubercule bacillus. Momentous discovery as this was, an ultimate cure for the disease would not come for well over half a century later. For Sophie Munch and the Bronte sisters and countless others now forgotten to history the only relief from the protracted torments of the white death were the laudanum bottle and their religion.

Tuberculosis was finally conquered in 1947 with the introduction of the age of antibiotics. To the industrialised "First World", the White Death has largely become a distant memory. Yet in the third world today it remains as big a scourge as it was to the first during the 19th century. In the 19th century it was the unsanitary conditions and rapidly expanding urban populations that came with industrialisation that was largely to blame for the spectacular emergence of the White Death at that time. Though a distant memory to us today we should not become complacent. The Grim Reaper of the 19th century has merely stepped back into its historical background shadows temporarily restrained but not defeated, biding its time to once again step into the light when the opportunity presents. We must keep in mind the conditions which would make this possible. Though the principles of sanitation are well understood at the dawn of the 21st century new threats in the form of HIV, multi-resistant organisms and the ease of international travel raise the spectre of a renewal of the battle with one of humanity's oldest adversaries - the "white death".

"The Sick Girl", oil on canvas, Christian Krohg, 1880-81, National Gallery, Oslo, Norway.

TUBERCULOSIS

Introduction

Tuberculosis (TB) is an important diagnosis to make.

Although now uncommon in Australia, it remains a major problem in global terms especially within the "third world". It is the number one infectious disease killer in the world and was so in the "first world" during the Nineteenth century. Very large numbers worldwide have "latent" TB.

It is an acute or chronic infection caused by the tubercle bacillus, Mycobacterium tuberculosis. Less commonly a similar clinical picture can be caused by M. bovis or M. africanum.

Initial pulmonary infection usually goes unnoticed with lesions healing, sometimes leaving traces of calcified scar tissue on CXR. The infection may however progress to pulmonary infection including miliary tuberculosis or through blood or lymphatic spread to produce extrapulmonary involvement.

The clinical features of TB will vary widely depending on the stage of the disease at presentation.

The most common scenario however for the ED will be the patient with respiratory symptoms.

The main issues will then be

- Risk stratification of the patient for TB.
- The decision to isolate and admit for further investigation.
- The decision to initiate treatment.
- Follow up of close contacts.

All suspected cases must be referred to:

- **The Infectious Diseases physician.**
- **The infection control nurse**

Pathophysiology

Organism:

The aerobic tubercle bacillus, **Mycobacterium tuberculosis** (human tuberculosis)

Mycobacterium bovis infects cattle to cause tuberculosis, but occasionally may also infect humans.

Pathogenesis:

Traditionally TB has been described as either primary or secondary with respect to pulmonary disease.

Primary disease:

This is usually seen in children not previously exposed to TB (or to BCG vaccination).

Bacilli within the lung generally survive initial cellular phagocytosis defence mechanisms, possibly due to their high lipid content capsules.

"Tubercule" formation occurs, (ie a granulomatous response to chronic infection) resulting in a "ghon focus". This most commonly appears as a 1-2cm sub-pleural lesion within the midzone region of either lung. Healing involves central "caseation" and fibrotic walling off of the lesion. Larger lesions may calcify.

Lymphatic spread from the ghon focus occurs to the pulmonary hilar lymph nodes resulting in tuberculous lymphadenopathy. The combination of ghon focus and hilar lymphadenopathy is known as the "primary complex".

Occasionally rupture of a ghon focus may occur resulting in a rapidly progressive pulmonary broncho-pneumonia.

During primary infection (or following BCG vaccination) the patient develops cell mediated immunity, (which can be demonstrated by a positive tuberculin skin test, a delayed hypersensitivity reaction to tuberculoprotein)

Secondary disease:

Secondary disease is thought to be due to either reactivation of "latent" primary TB or re-infection.

The usual site of secondary TB is the apex of the lung, or the apical segments of the lower lobes.

Extra-pulmonary spread may also eventually occur.

Lung lesions may:

- Cavitate and lead to a rapidly progressive pulmonary broncho-pneumonia or a more devastating "military" TB.

- Erode adjacent blood vessels leading to hemoptysis, which may be massive.

Complications

1. Pulmonary

- Cavitation. This is indicative of more advanced infection and is associated with a higher bacterial load.

- Tuberculous bronchopneumonia.

- **Miliary tuberculosis.**

  Miliary tuberculosis (TB) is the widespread dissemination of *Mycobacterium tuberculosis* from hematogenous spread, throughout the body, (not only the lungs).

- Haemoptysis, (which may be massive).

- Tuberculous effusions, (these appear to be due to hypersensitivity reactions rather than a direct result of the infection. AFBs are rarely recovered from pleural fluid)

2. Laryngeal

   - Laryngeal TB can lead to distressing symptoms, of cough and hoarse voice.

3. Renal

   - Chronic renal failure.

4. GIT

   - Nausea, vomiting and diarrhoea may occur.

   - Chronic inflammatory changes can lead to obstruction, adhesions and perforation.

   - It is usually a result of bovine TB acquired from unpasteurised milk or dairy products.

5. CNS

   - Tuberculous meningitis.

6. Lymph nodes

   - Chronic suppurative lymphadenopathy may occur, particularly of the cervical lymph nodes, (historically known as “scrofula”). Chronic sinuses may also arise from these.

7. Skeletal

   - Any bone may be involved but the most common site of involvement is the spine (historically, known as “Pott’s” disease).

8. Adrenal glands

    - Chronic adrenal insufficiency.

9. Genital

    - The testes and epididymis may be affected.
    - Chronic PID.

Risk Profile Factors

1. Demographic considerations:

    Recent immigrants and refugees from countries with a high incidence of tuberculosis, in particular:

    - Vietnam
    - India
    - China
    - Africa
    - Philippines
    - Eastern Europe
    - Pacific Islands

    Within Australia:

    - Aboriginal people and Torres Strait Islanders in some parts of Australia

2. Epidemiological considerations:

    - Those in close contact with a known case of active TB.
    - People living in substandard, overcrowded conditions.
    - Institutionalised people including prisoners.
    - Health professionals.

3. Immunosuppressed patients, in particular:

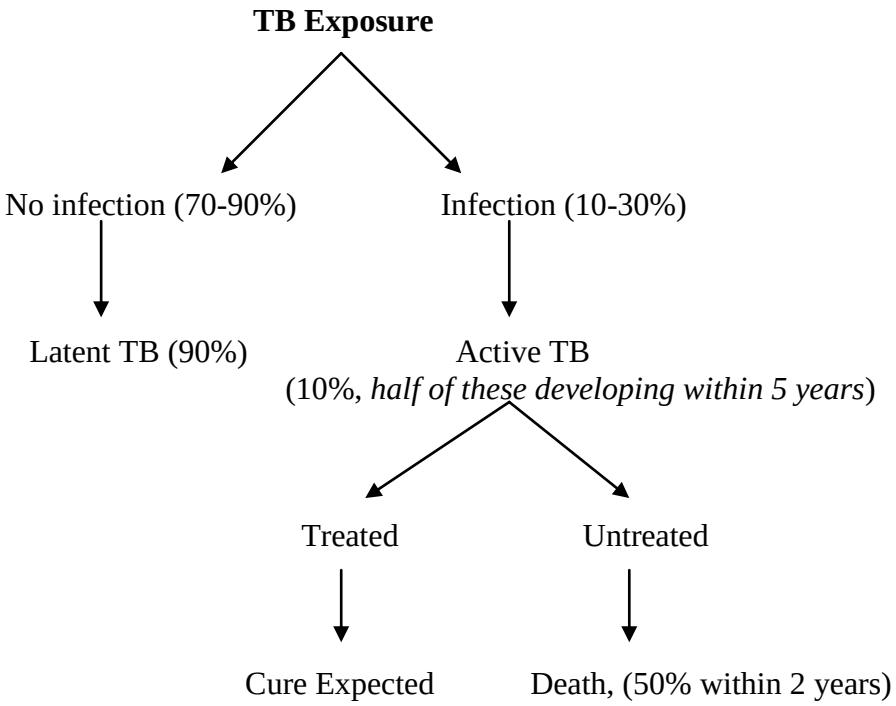
    - Those with HIV/AIDS
    - Patients on immunosuppressive agents.

- The malnourished.

and to a lesser degree:

- The elderly.
- Diabetics.
- Intravenous drug users.
- Alcoholics

Natural History of TB Infection [3]



Transmission

- TB is transmitted mainly by inhalation of infectious droplets produced by persons with **pulmonary or laryngeal** tuberculosis during coughing or sneezing.
- Invasion may occur through mucous membranes or damaged skin.
- Extrapulmonary tuberculosis, (other than laryngeal infection), is generally **not** communicable if not directly discharging.
- Urine is infectious in cases of *renal* tuberculosis.
- Bovine tuberculosis results mainly from ingestion of unpasteurised milk and dairy products. Aerosol transmission has been reported among abattoir workers.

- Note that person to person spread of other "atypical" (or "non tuberculous") mycobacteria is rare except in people who are immunosuppressed. These include M. avium intracellulare complex (MAC), M. kansasii, M. scofulaceum, M. marinum.

Degree of Infectivity:

In cases of pulmonary and laryngeal "open" TB the actual level of infectivity will be influenced by:

- Whether the sputum is culture positive.
- Whether the sputum is smear positive, including the degree of smear positivity, (ie the bacterial load)
- Whether a cavitating lesion is seen on CXR.

A case of culture positive, smear positive (with high bacterial counts) together with cavitating pulmonary disease is therefore highly infectious.

The following scoring system may be utilized to stratify the infectivity risk of a patient: [3]

Infectivity Score	Degree of Infectivity	Infectivity Parameter
0	Negligible	Extra pulmonary disease.
1	Low	Active pulmonary disease, with negative smears and culture negative
2	Medium	Active pulmonary disease, smear negative, but culture positive.
3	High	Active pulmonary disease and smear and culture positive. Or Culture positive cavitating pulmonary disease. Or Culture positive laryngeal disease.

An infectious active case of TB is defined as a case scoring 1 or more and a non-infectious case is defined as one with a score of 0. In general a patient with pulmonary TB who complies with therapy and does not have drug resistant disease should become non-infectious after 2-3 weeks of appropriate anti-tuberculous therapy.

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.

Period of Communicability

- In theory, the patient is infectious as long as viable bacilli are being discharged from the sputum.
- In practice, the greatest risk of transmitting infection is in the period prior to diagnosis of an open case.
- A sputum smear positive case is more infectious than a case only positive on culture.
- The risk of transmitting the infection is significantly reduced within days to two weeks after commencing appropriate chemotherapy.

Susceptibility and Resistance

- Everyone is susceptible to infection, however it is the immunosuppressed that are at greatest risk.
- The disease does not necessarily confer protective immunity as reinfection can occur.

Incubation Period

- Infection to the primary lesion or significant tuberculin reaction is about four to twelve weeks.

Reservoir

- Humans are the primary reservoir. Diseased cattle rarely act as reservoirs.

Clinical Features

The commonest presenting symptoms include:

- Chronic cough.
- Haemoptysis.
- Intermittent fevers and night sweats.

- Loss of weight.
- Severe “constitutional” symptoms, malaise, lethargy, anorexia.

Investigations

Blood tests

1. FBE
    - Anaemia of chronic disease is common in active cases.
2. U&Es/ glucose
3. CRP
4. LFTs
    - Anti-tuberculosis drugs may affect liver function.
4. HIV serology
    - All patients with TB should be considered for HIV testing.

Mantoux testing

Tuberculin (purified protein derivative or PPD) skin testing using the Mantoux procedure is a useful diagnostic aid for:

- Latent tuberculosis infection

False positives may occur with:

- Previous BCG vaccination.
- Previous non-tuberculous mycobacterium infection.

False negatives may occur with:

- Anergic individuals.

  This means individuals who do not mount an appropriate delayed hypersensitivity reaction or do so only very weakly. This can be seen in particular in patients with HIV/AIDS.

  Therefore, anergy testing is advised in cases where suspicion is warranted that it is present. Routine anergy skin testing is not recommended.
- Naturally waning immunity

High risk individuals who test negative should be considered for a second test (two step testing) after several weeks to confirm the result. Latent infection will usually show up as a positive reaction on the second test.

The test measures the *delayed type hypersensitivity* response, 48-72 hours after an *intradermal* injection of PPD. PPD is not mycobacteria species-specific. Note that it is not a test for *immunity* to TB.

The reaction is read by measuring the diameter of **induration** (palpable raised hardened area) across the forearm (perpendicular to the long axis) in millimeters. No induration should be recorded as 0 mm. Erythema (redness) should not be measured.

Interpretation of the result is complex and will depend on a number considerations including the patient's physical findings, CXR and risk profile. It should only be interpreted by specialists experienced in TB infection.

In general terms:

5 mm or more is positive in:

- HIV-positive person
- Recent contacts of an active TB case
- Persons with nodular or fibrotic changes on chest x-ray consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

10 mm or more is positive in:

- Recent arrivals (less than 5 years) from high-prevalence countries
- Injecting drug users
- Residents and employees of high-risk congregate settings (e.g., prisons, nursing homes, hospitals, homeless shelters, etc.)
- Mycobacteriology lab personnel
- Persons with clinical conditions that place them at high risk (immunosuppressed)
- Children less than 4 years of age, or children and adolescents exposed to adults in high-risk categories

15 mm or more is positive in:

- Persons with no known risk factors for TB

Quantiferon testing

Quantiferon is another method for testing for latent TB.

Note that tuberculin skin testing and quantiferon testing do not measure the same components of the immunologic response and are not interchangeable.

Assessment of the accuracy of these tests is limited by lack of a standard for confirming latent TB.

In comparison to Mantoux testing, quantiferon testing:

- Requires phlebotomy.
- Requires processing of the blood sample within 12 hours, (but the earlier the better)
- Can be accomplished after a *single* patient visit.
- Assesses responses to *multiple antigens* simultaneously.
- Does not boost anamnestic immune responses.
- Gives results that less subject to reader bias and error.

Quantiferon results are based on the amount of **gamma interferon** released from the patient's T lymphocytes in response to added tuberculosis antigens and compared to the amount of gamma interferon released with added mitogen, as a control. (If no gamma interferon in released by the patient's T lymphocytes in response to the control mitogen, then patient is "anergic" and the quantiferon test will not be interpretable.)

The utility of quantiferon testing in predicting the progression to "active" tuberculosis has not been evaluated.

Microbiology & Culture:

- Direct staining (using the Ziel-Nielsen or fluorochrome method) and culture of sputum (or other specimens) on appropriate TB media, for the presence of "Acid fast bacilli (AFB)", ie M. tuberculosis.
- Traditional mycobacterial cultures are slow growing and may require up to 8 weeks for growth and identification.

PCR:

- PCR testing can also be done on specimens.

CXR:

- A wide variety of appearances may be seen on CXR depending on the stage of the disease.
- Cavity formation is indicative of advanced infection and is associated with a high bacterial load.
- Non-calcified round infiltrates may be seen (and confused with lung carcinoma).
- Homogeneously calcified nodules (usually 5-20 mm) are tuberculomas and represent old infection rather than active disease.
- Miliary TB is characterized by the appearance of numerous small nodular lesions, resembling millet seeds.
- Patchy broncho-pneumonic consolidation.
- Tuberculous effusions may occur.

CT scan:

- This may help better define abnormalities in patients with indistinct findings on plain chest x-ray.

Making the Diagnosis

TB may be diagnosed by a consideration of a number of factors including:

1. The clinical features, (presenting symptoms together with risk factors)
2. Delayed hypersensitivity immunological testing:
    - The Tuberculin skin test using the Mantoux procedure.
    - The quantiferon test.
3. Radiographic examination CXR/ CT scan

Definitive diagnosis of TB rests on PCR testing and/ or the direct staining and culture of M. tuberculosis from sputum, urine, biopsy material, CSF or other clinical specimens.

A negative sputum test however does *not* rule out a diagnosis of TB.

Further information on tests for mycobacterium can be obtained from the Mycobacterium Reference Laboratory at Victorian Infectious Diseases Reference Laboratory.

Management

The index of suspicion for TB will depend on:

- The patient's symptoms and signs.
- Their risk profile.
- Their CXR findings, (cavitation in particular).

All suspected active and "open" (pulmonary or laryngeal) cases must be:

- **Referred to the Infectious Diseases physician.**
- **Referred to the infection control nurse.**
- **Nursed in a negative pressure isolation cubical, with appropriate barrier nursing.**
- **Admitted to hospital.**

Antibiotics

Adequate modern anti-TB chemotherapy for an appropriate period of time will result in an almost 100% cure rate.

Short treatment regimens have been in use for some years.

These most commonly involve the use initially of three or four drugs:

- Isoniazid
- Rifampicin
- Pyrazinamide
- Ethambutol

for two months, and continuing with isoniazid and rifampicin for a further four months.

Where there is evidence of drug *resistance* to isoniazid or rifampicin or to both, *short course* anti-TB chemotherapy is *inappropriate*.

The success of treatment relies heavily on patient compliance and direct supervision (or "directly observed therapy") should be the aim of any treatment program.

Compliance is also important to prevent the development of drug resistance.

Full prescribing details are listed in the current therapeutic guidelines however the exact regime will be determined by the infectious diseases consultant.

Dosette boxes should be used to assist in compliance with medication taking.

Multi resistant TB (MDRTB)

Resistance to at least isoniazid and rifampicin (whether or not it is also resistant to other drugs) is classified as multi-drug resistant. MDRTB is rare in Australia.

It has remained at less than two percent per year in the past 15 years.

There is however a potential risk of MDRTB in Victoria as most of the patients notified each year are overseas born, many from countries with high rates of drug resistant TB.

Isolation Issues:

- **Patients who present to the ED with suspected TB should be isolated in an appropriate isolation cubical. Appropriate infection control measures should be implemented, including the wearing of high filtration face masks by patient and staff.**

- With the introduction of potent anti-TB drugs, hospitalisation of tuberculosis patients is no longer mandatory unless social conditions or coexisting medical conditions dictate otherwise.

- Patients with pulmonary TB should be isolated either at home or in hospital until they **have been on adequate anti-TB therapy for 14 days and sputum smears are negative.**

- Appropriate education and counseling about minimizing the risk of transmission of infection should be provided to all patients, particularly those with pulmonary TB.

- There is no restriction on the movement of patients with non-pulmonary disease.

Control of Contacts

Exclusion of contacts is not necessary, unless they have signs and symptoms consistent with **pulmonary** TB.

Contact tracing and surveillance are the responsibility of the Department of Human Services and are managed by the TB Program. Anyone identified by health care workers as a contact of a case of TB should be referred to the TB Program.

Contact investigation consists of:

- History taking

- Tuberculin testing
- Radiographic examination.

The extent of investigation is governed by the characteristics of the source case. The scope of investigation is extended when the following factors in the source case are present:

- Acid-fast bacilli (AFB) in sputum smear and/ or culture.
- Cavitation on chest X-ray laryngeal TB
- Cough, particularly if productive of sputum
- Evidence of tuberculin conversion in any of the contacts.

Chemoprophylaxis may be appropriate for some contacts.

Vaccination [2]

- BCG (Bacille Calmette-Guerin) vaccination consists of a suspension of live M. Bovis.
- BCG vaccination has limited application in developed countries where the incidence of TB is low.
- It is not recommended for general use in the Australian community. This is because of the low incidence of TB in Australia and the **highly variable efficacy** of the vaccine in subjects above the age of 5 years.
- It should primarily be considered for specific high risk groups such as infants and young children travelling for extended periods to countries with a high incidence of TB. It is an effective vaccine in reducing TB meningitis and death in babies and children less than five years in countries of high TB prevalence.
- Protective effects of BCG may not last longer than 10 years.

For full indications and vaccination details refer to The Australian immunisation handbook, National Health and Medical Research Council.

Notification

- Tuberculosis (Group B disease) must be notified in writing within five days of diagnosis including clinical suspicion.
- All countries are required to report TB surveillance data to the World Health Organization. This data informs policies and strategies aimed at the global control of TB. Migrants and long term visitors to Australia are screened for evidence of TB prior to being granted a visa.

Contact Tracing

- This is carried out by the state Health Department.

School exclusion:

- Exclude until receipt of a medical certificate from the treating physician stating that the child is not considered to be infectious.

Additional Information Resources

- The Victorian Department of Human Services has a comprehensive handbook for the "Management, control and prevention of tuberculosis". A copy can be obtained by following the links in the article on tuberculosis on the "Bluebook" website.

Charlotte Bronte, chalk on paper, George Richmond, 1850.

References

1. The Blue Book Website.

2. The Australian Immunization Handbook, 8th ed 2003, p. 267-73.

3. Management, Control and Prevention of Tuberculosis Handbook, DHS 2002-2005

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4 September 2007