Management of tuberculosis

The management of tuberculosis is about responding to patient needs, making an accurate diagnosis, successfully treating a chronic disease and working in a team. It provides a model of how a quality health service should operate.

Doctors may believe they will hardly ever see a person with tuberculosis in their working lives. They may be right, especially if they live outside London or any other major city. However, all doctors want to provide the best health service possible, and the management of tuberculosis provides an opportunity to look at how this can be achieved. The directly observed therapy (DOTS) programme of the World Health Organization (*Table 1*) describes a general approach to organized health care.

The management of tuberculosis acts as a mirror for the quality of service. Equity of access is starkly revealed. Excellent diagnostic skills and appropriate use of tests are required. Adherence is a problem, as in other chronic diseases such as asthma, hypertension and human immunodeficiency virus (HIV) infection, where treatment is required even when, or especially when, a patient feels well. Teamwork is essential. Tuberculosis is largely a nurse-led service, but the team includes the physician, radiologists, microbiologists, administrative support, public health, community paediatricians, primary care doctors and many others outside the health service.

Tuberculosis: some relevant facts

If a person with influenza boarded a transatlantic flight, most people would be infected. If a person with tuberculosis made the same journey only 1% would be infected (McFarland et al, 1993) and perhaps 0.1% would develop active disease (Smieja et al, 1998). Tuberculosis requires prolonged exposure (>8 hours in the same room) to spread and is readily killed by ultraviolet light and desiccation. These facts explain why tuberculosis is found in those who live in overcrowded, poorly lit and inadequately ventilated accommodation. Such accommodation characterizes the poor and the dispossessed. Difficulty engaging with social and health services contributes to delayed presentation and transmission of disease.

Early diagnosis: reflections on a case history

The man discussed in this case report (see below) came to the accident and emergency department because he had no family doctor, was not registered with the health service and his poor English prevented him from any other access to health care. Almost half of those diagnosed with tuberculosis enter the health-care system through the emergency room (North East London Tuberculosis Network, unpublished data, 2007).

The symptoms of tuberculosis are relatively non-specific (*Table 2*). Community-acquired pneumonia is a common diagnosis, so it is difficult to know when tuberculosis should be suspected. Tuberculosis is more common in Eastern Europe than in the UK, as well as in most countries outside Europe and the Americas. The patient was homeless and, as suggested by his blood tests, alcohol formed a significant part of his calorie intake. In pneumonia, a raised white count and hypoxia are common (blood gases are not required unless the oxygen saturation on air is <91%; British Thoracic Society/Scottish Intercollegiate Guidelines Network, 2003), but both are rare in tuberculosis. Lower zone tuberculosis is more common in men with excess alcohol intake or diabetes and in women (Aktoğu et al, 1996).

A sputum smear is the quickest and easiest way to diagnose infectious tuberculosis. Sending sputum early can reduce the period of transmission and three samples cost about the same as a chest X-ray. However, the patient may be left with a sputum pot but given no instructions that sputum and not saliva is required. The sample may sit on the locker for some time before being sent to the laboratory. In areas where tuberculosis is

Table 1. Directly observed therapy strategy (DOTS)

Criterion	Example in UK	General application
Political commitment to tuberculosis control	Stopping tuberculosis	Government role in regulating health services
Diagnosis: especially by sputum smear	London standard: sputum smear result within 24 hours	Rapid diagnostic processes
Short course chemotherapy with supervision	Standard: National Institute for Health and Clinical Excellence guidelines	Evidence-based treatment
Reliable supply of free drugs	No free prescriptions (local arrangements to circumvent this) Problems with single drugs in last decade: pyrazinamide, streptomycin, cycloserine	Health care provided on basis of need rather than ability to pay
Adequate reporting system	Notification required Enhanced surveillance since 1998 Outcome monitoring*	Records/epidemiology for strategy and effectiveness of intervention

*Ditah et al (2008)

Dr Graham Bothamley *is Chair of the NE London TB Network Clinical Forum, Consultant Physician and TB Lead, Homerton University Hospital, London E9 6SR and Honorary Senior Lecturer at St Bartholomew's and the Royal London School of Medicine and Dentistry*

Case Report

A 42-year-old man was seen in accident and emergency with a cough and fever. He was given amoxicillin and clarithromycin for a community-acquired pneumonia and sent away. He returned 2 days later with the same symptoms. On this occasion, a chest X-ray showed an opacity in the left lower zone (*Figure 1*) and he was admitted. He was from Estonia and spoke only broken English. He was pyrexial (38.4°C), but otherwise seemed well. There was dullness at the left base. His oxygen saturation on air was 97% and a blood gas confirmed a pO2 of 10.4 kPa. A full blood count was normal apart from a mean corpuscular volume of 99 fl. His albumin was 30 g/litre with a globulin of 45 g/litre and aspartate aminotransferase 45 IU/litre. The admitting physician noted a pleural effusion and a diagnostic tap showed an exudate. Treatment for community-acquired pneumonia was continued. Sputum was sent for acid-fast bacilli. After 12 days on an open ward, he was transferred to a surgical centre discharge lounge to obtain his tablets before going to the homeless person's unit. While there, a positive sputum smear result was telephoned through to his medical team.

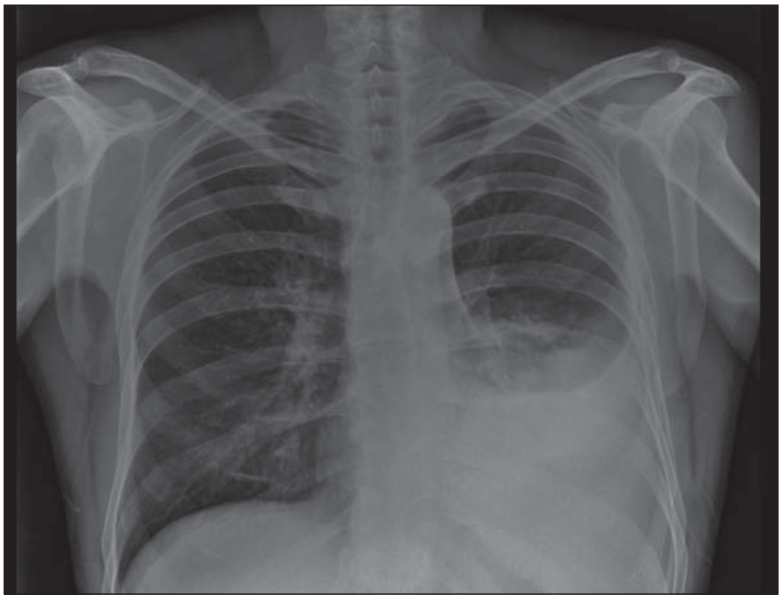

Figure 1. Chest X-ray from case report.

uncommon, samples for smear and culture may only be processed once or twice a week. Such problems are encountered with many diagnostic tests. Good clinical management includes explanation of a test, maintaining a procedure for the collection of specimens (e.g. night staff to collect urine and sputum samples before breakfast and before the ward collection takes place), appropriate delegation and acceptance of responsibility. Morning handovers between nursing and ward medical staff are important. Cost-effectiveness is governed both by the urgency of the situation and by the consequences of a delayed diagnosis.

Table 2. Symptoms of tuberculosis

Common, but non-specific	Cough >3 weeks
	Sputum >3 weeks
	Fever
	Weight loss
	Loss of appetite
	Malaise
Uncommon and more specific	Haemoptysis
	Night sweats
	Lymph node enlargement

Problems areas in the diagnosis of tuberculosis are upper lobe pneumonia, atypical presentations in the elderly, lymphocytic meningitis, all extrapulmonary tuberculosis and back pain as a result of tuberculosis of the spine or a psoas abscess (Weir and Thornton, 1985). Only if tuberculosis is considered will samples be sent for mycobacterial culture, the gold standard for the diagnosis of the disease. To avoid the problem of delayed diagnosis, all samples which require an invasive procedure (pleural and pericardial effusions, ascites, CSF and biopsies, especially from lymph nodes, pleura and peritoneum) should routinely be sent for mycobacterial culture.

The correct diagnosis

National surveys in England and Wales record that only 27% have a diagnosis of tuberculosis confirmed by sputum smear (43% of all pulmonary disease) and 60% by culture of the organism (Rose et al, 2001). Positive sputum smears are much less common in those with disease caused by environmental mycobacteria. The sensitivity of liquid culture has made false-positive mycobacterial cultures more common (perhaps as often as true tuberculosis), but molecular testing by the Mycobacterial Reference Units should give rapid identification of *Mycobacterium tuberculosis*-complex, a result that requires equally rapid communication to the attending physician – posting of results is unacceptable. Diagnosis of tuberculosis in children is most commonly associated with disease in their parents, siblings or guardians: a positive culture is infrequent (22%; Rose et al, 2001).

A positive culture is rare in those with a normal chest X-ray, except if there is concurrent HIV infection. If the patient is HIV-negative, a computed tomography (CT) scan should be undertaken to detect features consistent with tuberculosis, such as a small cavity or tree-in-bud appearance, before starting treatment. At least three sputum samples should be sent, as two positive cultures will lend greater certainty to the diagnosis.

The presence of caseating granulomas in material sent for histology is especially useful in those with extrapulmonary tuberculosis, including pleural disease. Material should be sent for mycobacterial culture, which cannot be undertaken if samples are sent in formalin. In those at risk of tuberculosis with clinical symptoms consistent with the diagnosis such as a pyrexia of unknown origin and raised inflammatory markers, a liver biopsy has a 60% chance and a bone marrow a 40% chance of detecting granulomas (Proudfoot et al, 1969). The use of

nucleic amplification assays is limited, their sensitivity is comparable with culture but much reduced in extrapulmonary disease (National Collaborating Centre for Chronic Conditions, 2006).

A diagnosis of tuberculosis remains unconfirmed by culture in more than a third of all notifications in England and Wales (Rose et al, 2001). Each hospital should have a lead physician for tuberculosis who can advise on the likely risk of tuberculosis and recommend treatment while the results of culture are awaited. Treatment should be continued even if the culture proves negative unless a firm alternative diagnosis is achieved. This ensures that tuberculosis can be excluded with relative confidence from the differential diagnosis should symptoms recur.

The tuberculin skin test can be used to enhance the suspicion of tuberculosis when the sputum smear and chest radiograph are clear. Reactions over 15 mm induration are considered significant and give a sensitivity of the Mantoux test of 83% in bacteriological confirmed disease and specificity of 91% (Chaparas et al, 1985). Similar sensitivity and specificity has been reported for the new interferon-gamma release assays used in the UK (Dosanjh et al, 2008). However, in the Gambia, sensitivities in active tuberculosis were less than in tuberculin skin testing, being 79% and 64% for the immunospot and enzyme-linked immunosorbant assay (ELISA)-based techniques respectively (Adetifa et al, 2007).

Infection control

Most patients with tuberculosis can be treated as outpatients. Patients with a positive sputum smear are the most infectious: those with a negative smear and a positive culture are estimated to be a fifth as infectious as those with a positive smear (Behr et al, 1999). However, coughing behaviour is very important. Even if a patient has a positive smear, simply covering the mouth with a hand or handkerchief significantly reduces the number of infectious particles released into the environment (Riley et al, 1959).

Medical admissions are either short for diagnostic purposes or lengthy because of social circumstances or multiple medical problems. The reasons to admit a patient with tuberculosis are given in *Table 3*. If admitted, patients require respiratory isolation, i.e. a single room, masks for patients and staff and appropriate negative pressure ventilation. Isolation should occur at the time when tuberculosis is considered in the differential diagnosis. Sputum samples for tuberculosis should not be collected on the open ward, in view of the susceptibility of ill patients, and especially of those with HIV infection, to tuberculosis (Kent et al, 1994). The number of infectious particles rapidly falls within days of starting treatment (Jindani et al, 1980) and patients are considered non-infectious after 2 weeks' treatment, although treatment is required for a minimum of 6 months to effect a cure.

Negative pressure rooms

Bronchoscopy and sputum induction should take place in a negative pressure room (defined as having more than six changes of air per hour) (Interdepartmental Working Group on Tuberculosis, 1996). Rooms with negative pressure are required for patients who are suspected of having tuberculosis resistant to both rifampicin and isoniazid (multidrug-resistant tuberculosis; MDRTB). Each emergency room should have a facility for isolation, not just because of tuberculosis but also to deal with other infectious diseases, such as haemorrhagic fevers in travellers from sub-Saharan Africa, and to limit transmission of new diseases such as severe acute respiratory syndrome (SARS). Each hospital should therefore also have at least one negative pressure room where such patients can stay until a diagnosis is obtained.

Treatment

Treatment should be effective and evidence based. All patients start treatment with four drugs – rifampicin, isoniazid, pyrazinamide and ethambutol – according to the National Institute for Health and Clinical Excellence (NICE) guidelines (National Collaborating Centre for Chronic Diseases, 2006). This ensures that single and multi-drug resistance should not affect outcome. All hospitals need a physician responsible for tuberculosis who can advise on whether other medication should be used, e.g. pyridoxine for those with HIV co-infection, alcoholism or malnutrition and steroids for meningitis, pericarditis and to prevent ureteric stenosis.

Directly observed therapy and adherence

All patients should have an equal opportunity to receive adequate treatment. An initial risk assessment for serious mental illness, drug resistance, previous non-adherence, alcohol and other drug addictions, young age, communications problem or learning difficulties can help decide whether treatment should be observed, usually as a three-times a week regimen. Homelessness should be addressed immediately by the local authority so that there is a fixed place of residence to administer treatment. In view of the

Table 3. Reasons for admitting a patient with suspected tuberculosis

Invasive investigations required	
Patient ill, e.g. tuberculosis meningitis	
Co-existent illness, e.g. liver disease, renal disease	
Communication problems	Language and cultural problems
	Addictions clouding sensorium
Prevent transmission of disease, e.g. patient shares a bedroom with a young child	
Place of safety, e.g. homeless or vulnerable	
Public Health Act 1984 sections 37 and 38	

public health risks from patients who remain infectious, there should be no restriction on the grounds of ineligibility as a result of failure to produce a birth certificate, asylum seeking, previously 'intentional' homelessness and the like. Personal support is beneficial in maintaining treatment for prolonged periods and this is best carried out by a named key worker who can be easily contacted by the patient.

Table 4. The tuberculosis team

Tuberculosis services	Lead tuberculosis physician
	GP
	Nurses: tuberculosis and general
	Administrator
	Microbiology
	Radiology
	Outreach worker
Tuberculosis networks	Lead tuberculosis network physician
	Negative pressure facilities for drug-resistant tuberculosis
	Local strategy
	Review of outbreaks and serious untoward incidents
	Audit and implementation of guidelines
	Mycobacterial Reference Units
Associated health services	Alcohol rehabilitation
	Drug addiction
	Mental illness
	Human immunodeficiency virus
	Advocacy
	Paediatricians
	Vaccination programmes
	Pharmacies
	Prison health
Local government	Environmental health
	Housing
	Social benefits
	Outreach workers
	Hostels
	Schools
Public health	Consultants in communicable disease control
	Surveillance, e.g. Health Protection Agency
	National guidelines (e.g. National Institute for Health and Clinical Excellence, British Thoracic Society)
	Legal services (use of Public Health Act)
	Outbreak management
	Port of health screening
	Mass X-ray units

Teamwork

The tuberculosis team includes a wide spectrum of skills (*Table 4*). Patient-centred health care is not only important for the management of tuberculosis, but understanding where tuberculosis ranks in the list of problems such patients may have is necessary if a cure is to be effected. The coordination of the different services can be complicated and the NICE guidelines recommend that a named key worker acts as the patient's advocate and ensures that all necessary services are accessed (National Collaborating Centre for Chronic Diseases, 2006). The same model can be used for patients with multiple medical problems or whose care requires the coordination of a number of services.

Public Health Act

About 1.5% of patients with tuberculosis in urban areas have such complex medical and social problems that adherence to treatment is almost impossible. In the past, many have been held in hospital under sections of the Public Health Act 1984, when they can be found or when they present to the emergency room. The current act deals only with the risk to the public and is not concerned with the fate of the individual with tuberculosis: there are no grounds for enforced treatment. Hospitals are not ideal places for such containment and a specialized facility would be appropriate.

Contact tracing

The assessment of contacts is an important part of tuberculosis control programmes and is common in other infectious diseases and also relevant to inherited disorders. Approximately 10% of all tuberculosis is identified by contact tracing and 1% (1000 per 100 000) of all contacts have tuberculosis (National Collaborating Centre for Chronic Diseases, 2006). Preventive treatment is important in the management of hypertension or reduction in smoking and barriers to adherence are similar. Those who are well can participate effectively in decisions regarding their health and extended roles of the tuberculosis team in public and personal education are important. In preventive treatment for tuberculosis, limiting the number of tablets (San Sebastian and Bothamley, 2000) and involvement in choosing regimens can improve adherence (Rennie et al, 2007).

The names of contacts should be recorded within 2 days of the diagnosis of tuberculosis and these contacts should be seen within 5 working days (Joint Tuberculosis Committee of the British Thoracic Society, 2000). These requirements can be compared with the receipt of referrals to outpatients and the flexibility required to see the patient within 14 days, e.g. in those with suspected cancer. Both require a responsive administration and adequately resourced outpatient departments.

Where resources are limited, priorities should be established. Europe is equally divided between services that see contacts of patients with pulmonary tuberculosis, on the

grounds of infectiousness, and those who see contacts of all those with tuberculosis, on the grounds of them being in a high-risk group (Bothamley et al, 2008). In the former instance, more than 8 hours' contact within a confined space is required for significant likelihood of transmission, whereas in the latter instance identification of the high-risk group is more important. Thus, household contacts of smear-positive patients are the first priority. This is closely followed by those with primary tuberculosis (e.g. mediastinal lymph nodes, pleural disease, miliary tuberculosis, tuberculous meningitis) where recent infection is likely and the infectious index case may be identified.

Other screening programmes

Foreign-born persons are screened in the UK as they constitute 64% of all cases of tuberculosis (EuroTB, 2008). Some are screened by chest X-ray through the Port of Health scheme, available only at Heathrow Airport, which requires that the person intends to be resident for more than 6 months. Few cases of active tuberculosis are detected. In high incidence areas, screening for tuberculosis at the new patient registration health check has proved fruitful (Griffiths et al, 2007). However, the prevalence of tuberculosis is lower in immigrants (*Table 5*) than in those with HIV co-infection, the homeless, prisoners, alcoholics and problem drug users (Story et al, 2007). Screening programmes should therefore be directed by local epidemiology with the aim of detecting latent tuberculosis infection (e.g. by tuberculin skin test or the newer blood tests).

Tuberculosis networks

More complicated tuberculosis may need advice from a tertiary centre. The organization of larger networks of hospitals (such as the North East London Tuberculosis Network) gives patients access to the best advice and parallels other formal structures to expedite referrals to tertiary centres in cancer and heart disease. A strategic role in developing standards, ensuring equity, sharing good practice and monitoring change through audit is important in planned commissioning. Networks should share facilities, e.g. negative pressure rooms where patients with drug-resistant tuberculosis can be treated. The management of patients with drug or alcohol addiction, HIV co-infection, neurosurgical complications of tuberculous meningitis or spinal tuberculosis can be helped by specialist teams which only larger centres would be able to provide.

Table 5. Relative prevalence of tuberculosis in London

High-risk group	Number	Denominator	Prevalence (per 100 000)
HIV infection	188	21 418	878
Homeless	29	10 024	788
Prison	29	5278	550
Alcoholism	158	88 780	178
Problem drug user	121	70 000	172
Recent migrant	297	200 000	149
Asylum seeker	387	420 000	92

Based on Story et al (2007)

Outbreaks and strain typing

Contact tracing is usually sufficient to identify small clusters of patients with tuberculosis. Rarely should casual non-household contacts be investigated for tuberculosis (National Collaborating Centre for Chronic Conditions, 2006). Strain typing has added a new dimension to the control of tuberculosis by identifying larger groups that are apparently unrelated (Moonan et al, 2006).

In the UK, an outbreak of tuberculosis was fortuitously identified by the concurrence of four patients with isoniazid resistance at a North London hospital. Strain typing confirmed their identity and since then there have been more than 325 cases identified by typing all cases of isoniazid resistance (Ruddy et al, 2004; M Yates, Mycobacterial Reference Unit, 2008), making this the largest outbreak in Europe over the last decade. This outbreak remains uncontrolled because of difficulties in contact tracing and the sub-culture of the social group affected, which includes those using crack cocaine, imprisoned and with chaotic lifestyles. This outbreak has highlighted the importance of non-household contacts, universal strain typing, the patient-centred approach for adherence which addresses needs with the same priority as the patient, the value of incentives and the pressing need for research into shorter courses of treatment for tuberculosis.

Conclusions

The management of tuberculosis services can appear daunting. However, the principles of responding to patient needs, designing a process to ensure a rapid and accurate diagnosis, successfully treating a chronic disease and working in a team are widely applicable. BJHM

Conflict of interest: none.

Adetifa IMO, Lugos MD, Hammond A et al (2007) Comparison of two interferon gamma release assays in the diagnosis of *Mycobacterium tuberculosis* infection and disease in The Gambia.

KEY POINTS

- Provide a patient-centred service.
- Send sputum early, when tuberculosis is first considered.
- Respiratory isolation for tuberculosis suspects in a side room is needed.
- Ensure each tuberculosis patient has a named key worker to coordinate care.
- Give directly observed therapy to those with complex needs.

BMC Infect Dis **7:** 122–31
Aktoğu S, Yorgancioglu A, Çirak K, Köse T, Derell SM (1996) Clinical spectrum of pulmonary and pleural tuberculosis: a report of 5,480 cases. *Eur Respir J* **9:** 2031–5
Behr MA, Warren SA, Salomon H et al (1999) Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet* **353**(9151): 444–9
Bothamley GH, Ditiu L, Migliori GB, Lange C (2008) Active case-finding in Europe: a TBNET (Tuberculosis Network European Trials group) survey. *Eur Respir J* **32:** 1023–30
British Thoracic Society/Scottish Intercollegiate Guidelines Network (2003) British Guidelines on the management of asthma. *Thorax* **58** (Suppl 1): i1–i94
Chaparas SD, Vandiviere HM, Melvin I, Koch G, Becker C (1985) Tuberculin test: variability with the Mantoux procedure. *Am Rev Respir Dis* **132:** 175–7
Interdepartmental Working Group on Tuberculosis (1996) *The prevention and control of tuberculosis in the United Kingdom. UK guidance on the prevention and control of transmission of 1. HIV-related tuberculosis 2. Drug-resistant, including multiple drug-resistant tuberculosis.* Department of Health, London Appendix D: 81–6
Ditah IC, Reacher M, Palmer C et al (2008) Monitoring tuberculosis treatment outcome: analysis of national surveillance data from a clinical perspective. *Thorax* **63:** 440–6
Dosanjh DP, Hinks TS, Innes JA et al (2008) Improved diagnostic evaluation of suspected tuberculosis. *Ann Intern Med* **148**(5): 325–6
EuroTB (2008) Country profiles. WHO European Region www.eurotb.org/rapports/2006/profiles.pdf (accessed 6 October 2008)
Griffiths C, Sturdy P, Brewin P et al (2007) Educational outreach to promote screening for tuberculosis in primary care: a clustered randomised controlled trial. *Lancet* **369:** 1528–34
Jindani A, Aber VR, Edwards EA, Mitchison DA (1980) The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *Am Rev Respir Dis* **121:** 939–49
Joint Tuberculosis Committee of the British Thoracic Society (2000) Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. *Thorax* **55:** 887–901
Kent RJ, Uttley AHC, Stoker NG, Miller R, Pozniak AL (1994) Transmission of tuberculosis in British centre for patients infected with HIV. *BMJ* **309:** 639–40
McFarland JW, Hickman C, Osterholm MT, MacDonald KL (1993) Exposure to *Mycobacterium tuberculosis* during air travel. *Lancet* **342:** 112–3
Moonan PK, Oppong J, Sahbazian B et al (2006) What is the outcome of targeted tuberculosis screening based on universal genotyping and location? *Am J Respir Crit Care Med* **174:** 599–604
National Collaborating Centre for Chronic Conditions (2006) *Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control.* Royal College of Physicians, London
Proudfoot AT, Akhtar AJ, Douglas AC, Horne NW (1969) Miliary tuberculosis in adults. *BMJ* **i**: 273–6
Rennie TW, Bothamley GH, Engova D, Bates IP (2007) Patient choice promotes adherence in preventive treatment for tuberculosis. *Eur Respir J* **30:** 728–35
Riley RL, Mills CC, Nyka W et al (1959) Aerial dissemination of pulmonary tuberculosis. A two-year study of contagion in a tuberculosis ward. *Am J Hyg* **70:** 185–96, reprinted *Am J Epidemiol* 1995; **141:** 3–14
Rose AMC, Watson JM, Graham C et al (2001) Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998. *Thorax* **56:** 173–9
Ruddy MC, Davies AP, Yates MD et al (2004) Outbreak of isoniazid resistant tuberculosis in north London. *Thorax* **59:** 279–85
San Sebastian M, Bothamley GH (2000) Preventive therapy: patients' perspectives in a multi-ethnic community. *Resp Med* **94:** 648–53
Smieja MJ, Marchetti CA, Cook DJ, Smaill FM (1998) Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Review (21 Nov 1998) In: The Cochrane Library, Oxford
Story A, Murad S, Roberts W et al (2007) Tuberculosis in London: importance of homelessness, problem drug use and prison. *Thorax* **62:** 667–71
Weir MR, Thornton GF (1985) Extrapulmonary tuberculosis. Experience of a community hospital and review of the literature. *Am J Med* **79:** 467–78