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Tuberculosis and the older patient

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Summary

Tuberculosis (TB) rates in the UK have increased by about 25% over the last 20 years. About 12% of cases occur in those over 65. Their diagnosis and treatment is similar to that of younger patients, but their presentation is often atypical, diagnosis is often delayed, there is a higher frequency of treatment side-effects and there is greater potential for drug interactions. Mortality increases markedly with age and more than half of those aged 80 years or more die before completing treatment. About 75% of TB in older patients is due to reactivation of latent disease acquired in childhood. The risk of reactivation is particularly increased by human immunodeficiency virus (HIV) infection and anti-tumour necrosis factor (anti-TNF) medication. Active disease spreads by the inhalation of airborne droplets, particularly in enclosed environments such as nursing homes. Interferon gamma release assays (IGRAs) are an important new development in recognizing latent infection. They should allow better targeting of treatment in those with recently acquired infection, or who are at risk of reactivation. With appropriate effort it should be possible to substantially reduce TB rates to fewer than 1 per million per year, the current US target.

Keywords: tuberculosis, ageing, interferon gamma release assay, epidemiology, management.

Epidemiology of TB and risk factors

The incidence of TB, the disease caused by infection with *Mycobacterium tuberculosis*, fell dramatically during the 20th century in the UK and other industrialized countries, reaching a nadir of approximately 11 cases per 100,000 in 1987.[1] Since then the UK rate has increased by about 25%[2] and TB is again a matter of public health concern. Initially the rise in incidence was associated with the HIV epidemic but, more recently, movement to and from high incidence countries has been largely responsible. Currently 72% of TB in the UK occurs in those born abroad.[2] Tuberculosis rates remain very high in many countries, particularly in Asia and Africa, and worldwide it is the commonest fatal infectious disease, with almost 2 million deaths per annum.[3]

Infection with *Mycobacterium tuberculosis* gives rise to clinically obvious disease in only about 5–10% of cases.[4] Most individuals mount a strong cellular immune response that suppresses the growth of the mycobacteria and contains them within granulomas, but does not eradicate them. Latent infection may then persist indefinitely, with a risk of reactivation if the immune response fails because of age, immunosuppression or co-morbidity. Occasionally, untreated but inactive infection can be recognized from incidental chest radiograph abnormalities such as upper zone fibrosis or calcified primary foci. More often, it is detectable only from the persisting immune response, either by a positive skin reaction to injected tuberculin protein (e.g. the Mantoux test) or more recently by IGRAs, *in vitro* tests for latent TB.

Latent TB is very common in countries with a high incidence of active disease with, overall, one-third of the world's population believed to be infected.[3] In industrialized countries where current TB incidence is low, latent infection is likely to be most common in older individuals. It is estimated that more than 90% of the population born before the 1950s had contact with TB and many, if not most of these, were infected.[5,6] Epidemiological studies of latent TB using skin tests do not properly reflect that and show peak prevalences at around age 40.[7] However, the Mantoux test becomes less sensitive with age. For example, only 25% of those above 80 years with active disease have a positive response, compared with 70% of younger individuals.[8] The pattern of skin responses in the population thus probably reflects a balance between increasing latent TB rates with age and diminishing immunological responses. There have been no population studies using other methods of diagnosing latent TB and so its precise prevalence in older age, and the associated risk of reactivation, is unknown. It might be that, in some individuals, the mycobacteria eventually die and the latent

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infection clears. More probably, a diminishing systemic immune response with age contributes to the risk of reactivation.

In the past it was thought that more than 90% of TB in adults arose because of reactivation of latent disease.[9] More recent studies, using molecular typing techniques, have shown that 30–50% of cases occur in clusters with identical strains, suggesting recent transmission from an infected source.[10,11] Clustering is much less common in older people, in whom about 75% of cases do appear to be due to reactivation of latent disease.[10–12] Reactivation of latent disease thus explains the increased risk of active TB with age. This is shown clearly in statistics from the USA[13] and until recently was apparent in national statistics from England and Wales.[14] Currently the British figures are overwhelmed by the high incidence in younger individuals born abroad.[2] Although only around 12% of TB occurs in those over the age of 65 years,[2] they are an important group as they often have disease that is more difficult to diagnose and treat, and they have substantially higher mortality than younger cohorts.

Active TB is approximately twice as common in men compared with women,[12] in smokers,[15,16] in diabetics[17,18] and in those who are malnourished.[19] HIV infection increases the risk 20- to 40-fold and is now responsible for 10–20% of all TB worldwide.[20] At present 8% of those with TB in England and Wales are co-infected with HIV,[21] but the rate varies considerably in relation to known risk factors, and is less than 1% of those over 65 years.[21] The rate of co-infection in older people is higher in the USA, at approximately 3.6%.[22] The survival of those with HIV continues to increase and approximately 25% of those infected are now aged 50 or more.[23] Continued vigilance for TB in this group will be necessary. It is recommended that HIV testing is carried out on everyone diagnosed with TB.[24]

Tumour necrosis factor α (TNFα) is a lymphokine which, in animal models, plays an important role in the formation of granulomas and the containment of TB infection. Anti-TNFα medications are now widely used in the treatment of inflammatory joint, bowel and skin disease. The mean age of those on treatment in Britain is 55 years[25] and the medications are often used in older individuals. They are associated with an increased risk of TB that appears to be largely due to reactivation of latent disease.[26] The monoclonal antibodies infliximab and adalimumab are associated with at least a 10-fold increased risk.[27] The fusion protein etanercept that binds free TNFα has a lower risk, possibly because it has less effect on membrane-bound TNFα in granulomas.[27] Current recommendations are that all patients are screened for latent TB and treated appropriately before commencing anti-TNFα therapy.[28]

TB spreads by the inhalation of airborne droplets from infected individuals: infection rates are approximately doubled in confined communities such as prisons and nursing homes. Hutton reported TB rates in US nursing home residents that were 1.8 to 5.7 times those of age-matched community residents with almost twice as many cases identified only at death.[29] Similar findings have not been generally reported from the UK,[30] though outbreaks affecting up to 20% of nursing home residents have been described.[31] About 4.5% of those over 65 years and 20% of those over 85 years live in nursing homes[32] and they represent a vulnerable group in whom TB infection can spread rapidly. The risks extend to employees who are at approximately 3-fold increased risk of TB.[33]

Tuberculosis is caused by mycobacteria belonging to the *M. tuberculosis* complex: principally *M. tuberculosis*, occasionally *M. bovis*, and rarely *M. africanum*. There are many other non-tuberculous mycobacteria (NTMs) that are common in soil and water and are of low human pathogenicity. They can occasionally cause infection, particularly in those who are immunocompromised because of HIV infection. Mycobacterium avium complex (MAC) is the commonest and appears to be an increasingly common cause of disease in previously healthy older people, particularly females.[34] There is otherwise no association between NTM infection and age. The clinical and radiological features are similar to those of TB, and antituberculosis medication is often started following a positive smear before the correct diagnosis is established from mycobacterial culture. Diagnosis is sometimes uncertain as NTMs can contaminate sputum samples and even laboratory water supplies. Treatment can be difficult as the organisms are generally resistant to several antituberculosis drugs, but person-to-person infection does not occur and so there is no need for isolation or for contact screening procedures.

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Clinical features, investigations and diagnosis

The presentation of TB in older people is similar to that in younger adults except that the typical symptoms of fevers, night sweats or haemoptysis are more likely to be absent. Non-specific symptoms, such as malaise, dyspnoea or altered mental state may predominate.[35,36] The radiological appearances may also be less specific: cavitation is less common and miliary disease is more common.[37] These features probably reflect relative lymphopaenia in older individuals, as similar atypical presentations are common in those with HIV infection.[38] They make the diagnosis more difficult and probably contribute to diagnostic delays. Greenaway, in a study of 17 North American hospitals, found that the diagnosis of TB was initially missed in 45% of 430 hospitalized patients. Age was the strongest predictor, with diagnostic delay being eight times more common in those aged 80 years or above. This led to an average delay to isolation of 12.5 days, increased mortality and a suggestion of an associated increase in infection rates in staff.[39] Wallace recently highlighted the increasing frequency with which TB patients are presenting with advanced disease and demonstrated that this was more common in areas where TB incidence was low.[40] These studies emphasize the need for continued vigilance.

Culture of *M. tuberculosis* is the definitive method of diagnosing active infection and should be attempted whenever possible. In practice, a positive culture is only achieved in about two-thirds of cases of pulmonary TB and in fewer than half of non-pulmonary disease.[2] Often treatment has to proceed on the basis of clinical, radiological or histological findings. Occasionally the diagnosis is based on the unexpected finding of caseating granulomas on a biopsy, and surgeons should be prompted to send specimens for culture whenever TB is a possibility

When the number of organisms in a specimen exceeds 5000 per millilitre they can usually be seen on direct microscopic examination and the specimen is said to be smear positive.[41] The traditional Ziehl-Neelsen stain is now rarely used, having been superseded by auramine or immuno-fluorescent techniques. Lower mycobacterial counts cannot be detected from the smear, but they can usually be grown on appropriate culture media. Traditional solid media are now generally supplemented by liquid media labelled with ^{14}C. Actively metabolizing organisms convert the ^{14}C to radiolabelled CO_2, allowing growth to be detected with greater sensitivity, and in 10–14 days rather than the 2–6 weeks required with conventional media.[4] It is usually appropriate to start medication if a smear is positive for acid-fast bacilli, but treatment may need to be modified if the organism is non-tuberculous or if drug resistance is identified.

The sputum smear is positive in more than half of pulmonary TB cases, though not always on an initial specimen. Three sputum samples should be obtained routinely if TB is suspected.[4] Additional techniques such as sputum induction with hypertonic saline[42] or bronchoscopy with bronchial washings[43] can be used. They are likely to identify additional cases,[43] but they carry a greater risk of transmission of infection to hospital staff and other patients. In non-pulmonary disease, appropriate samples such as lymph node aspirates or early morning urine specimens may be required.

Amplification of mycobacterial DNA using polymerase chain reaction (PCR) techniques can be used to speed identification. The usefulness of the technique is limited by the presence of inhibitors in body fluids and the sensitivity is only 50–70% in smear-negative specimens[44] and in some studies has poor specificity.[45] Sensitivity is greater at about 95% in smear-positive samples[44] and in mycobacterial cultures. This allows early differentiation of *M. tuberculosis* from NTM and can be useful in guiding initial treatment, particularly in the immunocompromised, or in determining the need to embark on a contact-tracing programme. Further probes can identify the genes that code for rifampicin and isoniazid resistance.[46] The former, in particular, has high sensitivity and specificity[47] and is useful in guiding initial treatment if drug resistance is suspected.

The tuberculin skin test has been used for many years to identify TB infection, particularly in its early or latent stages. Purified tuberculin protein is injected intradermally and the degree of delayed hypersensitivity is quantified from the subsequent skin swelling.[48] In the past the Heaf test was widely used in the UK but now only the Mantoux test is available. It has a number of significant limitations. Intradermal injection is not always carried out properly and there is variability between readers in measuring the skin swelling.[49] The result is read at 48–72 hours and that does not lend itself to weekly clinic organization. False positive

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reactions can arise from exposure to NTMs and this has led to the investigation of a number of TB pseudoepidemics.[49] Prior BCG immunization also results in a positive response. False negative reactions occur with immunosuppression, active TB and advanced age.[50] An immune response can be stimulated by the test itself and, particularly in older patients, an initially negative response can become positive when repeated, giving the false impression of recent infection.[51]

The recent development of *in vitro* diagnostic tests has been a major advance in identifying latent TB.[52] These tests identify interferon gamma release from lymphocytes stimulated with the *M. tuberculosis*-specific peptides early secretory antigen (ESAT-6) and culture filtrate protein (CFP-10). There are currently two commercially available tests: QuantiFERON-TB-2 Gold (Cellestis Ltd; Carnegie, VIC, Australia) uses an enzyme-linked immunosorbent assay on the supernatant from stimulated lymphocytes, and T-SPOT.TB (Oxford Immunotec; Oxon, UK) uses an immunospot assay to detect and count individual stimulated T lymphocytes.

IGRAs have the practical advantages over skin tests that they are not observer-dependent and a result can be obtained following a single clinic visit. They do require careful handling of the samples to ensure that viable lymphocytes are transferred to the laboratory. Indeterminate results can be obtained in up to 20% of samples particularly in the presence of lymphopaenia[6,53] and can limit their usefulness in older people.[54] Overall, they do appear to be less affected by age than the tuberculin skin test.[8]

The major advantage of IGRAs over the Mantoux test is that ESAT-6 and CFP-10 are not expressed by BCG or by most NTMs and so a positive response is much more specific for *M. tuberculosis*.[55] Because of the anergy produced by active TB, IGRAs are negative or indeterminate in up to 15% of cases of active disease and are of little diagnostic value in that setting.[8,55,56] They should not be used to diagnose or exclude active TB.

The main use of IGRAs is in identifying latent TB that has a risk of progressing to active disease. The prevalence of positive tests is closely related to the risk of infection in situations such as TB outbreaks.[57] IGRAs have a low false positive rate (3–8%) in individuals unlikely to have TB,[58] suggesting that the tests are valid, but their precise sensitivity and specificity in identifying those at risk of active TB has yet to be determined. Diel recently demonstrated that 11% of 601 contacts who had 40 or more hours exposure to TB patients were IGRA positive. Six went on to develop active TB over the course of the next 2 years, all from the group who were IGRA positive and declined chemoprophylaxis.[59] IGRAs are designed to identify effector T cells that are being actively stimulated by exposure to *M. tuberculosis* rather than memory T cells and so they should become negative after treatment. However, up to two-thirds of tests remain positive after treatment, at least over the course of 6–12 months.[60,61] Thus while initial experience with IGRAs is encouraging, their precise role and usefulness remains to be determined.

Management of TB

TB treatment is prolonged and complex. The duration of therapy must be sufficient to eradicate slowly dividing intracellular organisms, and several drugs are needed to avoid the development of resistance. The current optimum regimen comprises 2 months quadruple therapy with pyrazinamide, ethambutol, rifampicin and isoniazid, followed by 4 months with rifampicin and isoniazid.[4] It is highly effective with cure rates exceeding 95% and a subsequent relapse rate of less than 3% if taken properly.[4] Longer regimens may be needed if there is extensive disease[62] and are recommended for meningeal TB. Corticosteroids are added for meningeal disease and sometimes in other forms of TB.[4]

TB treatment requires oversight by someone with appropriate experience, preferably in a dedicated clinic with a multidisciplinary team approach. Combination products are used with similar names that can be easily confused; doses vary with weight; and there is a risk of serious adverse effects. One study reported treatment errors in 15% of cases, but these were seven times more common in non-specialist centres.[63] Considerable efforts are often needed to ensure compliance, particularly with groups such as recent entrants to the country who do not speak the local language, or drug addicts and the mentally ill who are poorly integrated with medical services. Directly observed therapy (DOT) is an important strategy that is widely used in resource-poor countries and is generally recommended for those

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with drug-resistant disease or in whom there is a risk of non-compliance.[4] It may be useful for older people with memory problems or who use multiple additional medications. In this setting it may be most useful for a family member to supervise the therapy, with appropriate health worker support. TB medication is exempt from prescription charges in the NHS, when prescribed in a specialist TB centre.

M. tuberculosis is subject to a spontaneous mutation that confers rifampicin resistance at a rate of approximately one per 5 billion organisms per generation.[64] Resistant organisms are at a metabolic disadvantage and generally do not thrive,[65] but monotherapy is likely to induce resistance because of the very large numbers of organisms in those with active disease. Resistances to other antituberculosis agents occur at a slightly higher rate, but they are genetically independent and the probability of spontaneous resistance to more than one agent is very low. Drug resistance develops because of inadequate treatment and that is often a consequence of physician error: either the initial regimen is inadequate or a single agent is added to a failing regimen.[66]

Primary resistance occurs when someone is infected by an already resistant organism. It is less common with age, affecting 2% of cases over 65 compared with 7% of younger patients.[2] That is in part because TB in older individuals is often caused by reactivation of disease that was acquired before the introduction of antibiotic chemotherapy. Multiple drug-resistant tuberculosis (MDR-TB) is resistant to at least isoniazid and rifampicin. It occurs in 1.1% of cases but is rare in those over 65 years. Extensively drug-resistant tuberculosis (XDR-TB) with resistance to second-line agents is increasingly reported.[2] Treatment of MDR-TB generally involves five drugs for two years and adds hugely to the costs of managing the disease and the morbidity. Considerable resource should be employed to prevent it occurring.

Antituberculous chemotherapy causes serious side-effects sufficient to require interruption of treatment in 9% or more of patients.[67–69] Older people are at greater risk[67] on account of co-morbidities, age-related changes in drug metabolism, and increased use of other medications with the potential for interactions. Hepatitis is the commonest problem and occurs with isoniazid, rifampicin and pyrazinamide.[68] The risk increases with age, at least with isoniazid, and is 2–8 times more common in those over 60 years.[70] Generally, hepatitis is reversible if detected early but it can be severe or fatal if treatment is continued[70] and so surveillance is mandatory throughout treatment. The reason for the increased risk of hepatitis with age is not entirely clear: isoniazid pharmacokinetics are markedly affected by acetylation status,[71] but do not change with age.[72] Reduced activity of excretory pathways is probably responsible and there is probably less binding to albumin with higher free drug concentrations.[73] Other independent risk factors for hepatotoxicity include a history of hepatitis, low body mass index (BMI) and the presence of diabetes mellitus.[71]

Rifampicin is a potent inducer of liver cytochrome P450 and so interacts with a number of other drugs. The commonest clinically significant problems are decreased effectiveness of oral contraceptives, oral corticosteroids, warfarin, digoxin, phenytoin, calcium channel blockers, beta-blockers and sulfonylureas. Doses of oral corticosteroids generally need to be doubled to maintain effectiveness.

Isoniazid binds to pyridoxine (vitamin B6) to form a hydrazone that is excreted in the urine. This can cause deficiency which manifests as a peripheral neuropathy, particularly in diabetics, alcoholics, the malnourished or those with renal failure. The neuropathy can be prevented by pyridoxine supplementation during treatment. There is no clear evidence that older people are more prone to isoniazid neuropathy than others. Ethambutol can cause optic neuropathy but that is rare at current doses. There is a range of other uncommon potential side-effects.

The overall mortality rate from TB amongst those undergoing treatment in the UK is low, at approximately 2 per 1000,[2] but there is additional mortality from co-morbid conditions. Both death from TB and death from co-morbid conditions are strongly associated with age. TB mortality is 20 times higher, at approximately 5%, in those aged 65 years or more.[2,74] Older patients with TB have higher prevalences of cardiovascular disease, diabetes, malignancy and previous gastrectomy, and five times as many die from co-morbid conditions.[35] The overall fatality rate before the completion of treatment is 26%.[2] It increases progressively with age, exceeding 50% in those over 80 years. The diagnosis of TB in an older person thus carries a very poor prognosis. Other recognized poor prognostic factors include the

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presence of end-stage renal failure, malnutrition, immunosuppression, respiratory failure,[75] HIV[76] and diabetes.[77]

Treatment of latent TB

The treatment of latent TB is often referred to as chemoprophylaxis, but that nomenclature is potentially misleading. The drugs used are the same as with active disease, but because the number of viable organisms is several orders of magnitude lower, fewer drugs and shorter regimens can be used. Most evidence of efficacy comes from studies of isoniazid that reduces the risk of infection by about two-thirds after six months of treatment.[78,79] Three months of treatment with rifampicin and isoniazid probably has similar efficacy.[80]

The pharmacological side-effects of treating latent TB are no less than those associated with the treatment of active disease and may even be slightly greater,[81] possibly because the immunosuppression of active TB reduces drug toxicity. Because the incidence of isoniazid-induced hepatitis increases with age and reaches 3% in those aged 50 years or more,[67,82] treatment is often not offered to those over 35 years.[4] In one US study, only 50% of patients considered eligible were treated for latent TB, with age as the commonest stated reason for not offering therapy.[83] However, most isoniazid-induced hepatitis is mild, and with appropriate surveillance and early detection should be reversible, and so the justification for limiting treatment to younger patients has been questioned.[9]

Compliance is often a problem in treating latent TB as those who are clinically well are required to take regular medication for prolonged periods to prevent a disease that is, in any case, unlikely to develop. Less than one-third of patients have completed a full course of treatment in some studies.[84] A perception of a low risk from TB and dislike of venepuncture were cited as the main reasons for discontinuing. With poor compliance there is at least a theoretical risk of inducing drug resistance that might make treatment of subsequent active disease more difficult.[85]

In the US, the incidence of TB has more than halved, from a rate of 10.5 per 100,000 in 1992 to 4.2 in 2008.[13] This has been attributed, in large part, to an active policy of diagnosing and treating latent TB. Groups considered to be at risk include those with recent contact with active TB, immigrants, and patients with HIV and other conditions that increase their susceptibility. The advent of improved immunological methods of detecting latent TB using IGRAs should allow better targeting of these groups. It may also allow extension of the populations considered for treatment, nursing home residents being a potential target. This group is at increased risk of TB, but currently there are no standard recommendations for managing latent infection when it is detected. The American Thoracic Society includes them amongst those in whom targeted treatment is appropriate[86] and there are strong advocates of aggressive management of latent TB in this group.[87] However, the Advisory Committee for the Elimination of Tuberculosis and the American Geriatric Society stop short of recommending routine treatment of latent TB, preferring screening of nursing home residents for TB at entry, repeat annual clinical evaluations, and further TB testing and treatment if clinically appropriate.[88]

Prevention, isolation and control of TB

Most immunizations work by inducing antibodies, but these are of little or no importance in protection against TB, which is dependent on lymphocyte function. It is therefore not surprising that no fully effective vaccine has yet been developed. Bacille Calmette-Guerin (BCG), a live attenuated form of *M. bovis*, confers some protection but its efficacy has varied considerably in a number of large studies and in some it has shown no effect.[89] Overall, it probably confers around 70% protection in childhood, with particular effectiveness against tuberculous meningitis.[4] Its protection wanes with time and is no longer evident after about 10 years.[90] There is no good evidence that reimmunization, or immunization of adults, has any effect.[91] The UK school BCG programme was disbanded because of lack of cost-effectiveness and immunization is currently restricted to high-risk groups including health care workers and some neonates.[4] The limited efficacy of BCG has driven a search for novel vaccines with greater efficacy and several are currently under investigation.

Preventing active disease by immunization and the treatment of latent infection are important strategies in the control of TB. Prompt diagnosis,

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the early institution of correct treatment and the prevention of onward spread of infection are also vital. Because of the efficacy of modern chemotherapy, prolonged isolation is no longer necessary but contact screening procedures are generally employed to identify the source of infection and any additional cases. The risk of infection is determined by the infectivity of the index case and by the frequency and duration of contact, particularly in poorly ventilated indoor settings. Smear-positive patients are about five times more infectious than smear-negative patients,[16,59] and coughing is an important risk factor, particularly if there is cavitatory disease. Those with TB in organs other than the lungs are rarely infectious, nor are those with latent tuberculosis. The numbers of viable bacilli in sputum fall rapidly with the initiation of treatment[92] and patients are unlikely to be infectious after 2 weeks of chemotherapy.

Patients with TB are likely to have been unwell and potentially infectious for several weeks before the diagnosis is established. The average contact of those selected for screening was in the region of 250 hours in the 3 months preceding the diagnosis in one study,[16] and that was associated with an approximately 20% risk of infection as detected by a positive tuberculin skin test[16,93] and a 1% risk of active disease.[16,94] Thus each hour of exposure is associated with something in the region of a 1:1000 risk of infection and a 1:10,000 risk of active disease in the short term. In the UK it is generally held that 8 hours of exposure poses sufficient risk to justify screening.[4] Hospital staff are at increased risk of TB,[4,95] though the absolute risks are low. The arrival of a patient with TB on a hospital ward often engenders high levels of anxiety, but in most circumstances nursing a patient in a side-ward, with masks used when any sputum-inducing procedures are carried out, provides sufficient protection.[4] Individuals with MDR-TB need to be treated with greater caution and nursed in appropriate isolation facilities in a negative pressure room. Some individuals are particularly infectious and occasionally extensive screening programmes have to be undertaken.[96]

As most cases of tuberculosis in England and Wales now occur in those born abroad,[2] screening of new entrants to the country is an important part of a TB control strategy. There is no systematic targeting of other high-risk groups such as rough dwellers or intravenous drug users, though some *ad hoc* programmes have reported successes.

Controlling TB remains a challenge, but in an economically developed country it should be possible to reduce rates considerably from their current levels to less than one per million.[97] Improved diagnostic tools and targeting of treatment will help but clinical vigilance, prompt diagnosis and carefully supervised treatment will remain important. Older patients are an important group because of their high prevalence of latent infection, their increased risk of developing active disease, their often atypical and delayed presentation, their increased risk of treatment side-effects, and ultimately their greater mortality from the disease.

Conflicts of interest

The authors had no conflicts of interest to declare.

References

1 Hayward A, Watson J. Tuberculosis in England and Wales 1982–1993: notifications exceeded predictions. *Communicable Dis Rep* 1995; **5**: R29–33.

2 Tuberculosis in the UK: Annual report on tuberculosis surveillance in the UK 2009. London: Health Protection Agency Centre for Infections, 2009.

3 Dye C, Scheele S, Dolin P, Pathania V, Raviglione M. Global burden of tuberculosis. Estimated incidence, prevalence, and mortality by country. *JAMA* 1999; **282**: 677–86.

4 National Collaborating Centre for Chronic Conditions. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: Royal College of Physicians, 2006.

5 Rieder H. Epidemiology of tuberculosis. In Gibson G, Geddes D, Costabel U, Sterk P, Corrin B (eds). *Respiratory Medicine*. Saunders, 2003, pp. 938–943.

6 Mori T, Harada N, Higuchi K, Sekiya Y, Uchimara K, Shimao T. Waning of the specific interferon-gamma response after years of tuberculosis infection. *Int J Tuberculosis Lung Dis* 2007; **11**: 1021–25.

7 Bennett D, Courval J, Onorato I, Agerton T, Gibson J, Lambert L *et al.* Prevalence of tuberculosis infection in the United States population: the national health and nutrition examination survey 1999–2000. *Am J Resp Crit Care Med* 2008; **177**: 348–55.

https://doi.org/10.1017/S0959259810000110 Published online by Cambridge University Press

8 Kobashi Y, Mouri K, Yugi S, Obase Y, Miyashita N, Okimoto N *et al.* Clinical utility of the QuantiFERON TB-2G test for elderly patients with active tuberculosis. *Chest* 2008; **133**: 1196–1202.
9 Stead W. Tuberculosis among elderly persons, as observed among nursing home residents. *Int J Tuberculosis Lung Dis* 1998; **2**: 564–70.
10 Geng E, Krieswirth B, Driver C, Li J, Burzynski J, Dellalatta P *et al.* Changes in the transmission of tuberculosis in New York City from 1990 to 1999. *New Engl J Med* 2002; **346**: 1453–58.
11 Yang Z, de Haas P, Wachmann C, van Soolingen D, van Embden J, Andersen A. Molecular epidemiology of tuberculosis in Denmark in 1992. *J Clin Microbiol* 1995; **33**: 2077–81.
12 France A, Cave M, Bates J, Foxman B, Chu T, Yang Z. What's driving the decline in tuberculosis in Arkansas? A molecular epidemiologic analysis of tuberculosis trends in a rural, low-incidence population, 1997–2003. *Am J Epidemiol* 2007; **166**: 662–71.
13 CDC. Reported tuberculosis in the United States, 2008. Atlanta, GA. US Department of Health and Human Services, 2009.
14 Rose A, Watson J, Graham C, Nunn A, Drobniewski F, Ormerod L *et al.* Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998. *Thorax* 2001; **56**: 173–79.
15 Bates M, Khalakdina A. Risk of tuberculosis from exposure to tobacco smoke. *Arch Intern Med* 2007; **167**: 335–42.
16 Aissa K, Madhi F, Ronsin N, Delerocque F, Lecuyer A, Decludt B *et al.* Evaluation of a model for efficient screening of tuberculosis contact subjects. *Am J Resp Crit Care Med* 2008; **177**: 1041–47.
17 Ponce-de-Leon A, Garcia-Garcia M, Garcia-Sancho M, Gomez-Perez F, Valdespino-Gomez J, Oliaz-Fernandez G *et al.* Tuberculosis and diabetes in southern Mexico. *Diabetes Care* 2004; **27**: 1584–90.
18 Leung C, Lam T, Chan W, Yew W, Ho K, Leung G *et al.* Diabetic control and risk of tuberculosis: a cohort study. *Am J Epidemiol* 2008; **167**: 1486–94.
19 Khan A, Sterling T, Reves R, Vernon A, Horsburgh R. Lack of weight gain and relapse risk in a large tuberculosis treatment trial. *Am J Resp Crit Care Med* 2006; **174**: 344–48.
20 Global tuberculosis control: surveillance, planning, financing. Geneva: World Health Organisation, 2007.
21 Ahmed A, Abubakar I, Delpech V, Lipman M, Boccia D, Forde J *et al.* The growing impact of HIV infection on the epidemiology of tuberculosis in England and Wales: 1999–2003. *Thorax* 2007; **62**: 672–76.
22 Albalak R, O'Brien R, Kammerer S, O'Brien S, Marks S, Castro K *et al.* Trends in tuberculosis/human immunodeficiency virus comorbidity, United States, 1993–2004. *Archives Intern Med* 2007; **167**: 2443–52.
23 Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2007: US Department of Health and Social Services Centers for Disease Control and Prevention, 2009: vol 19.
24 Pozniak A, Miller R, Lipman M, Freedman A, Ormerod L, Johnson M *et al.* BHIVA treatment guidelines for tuberculosis (TB)/HIV infection 2005. *HIV Medicine* 2005; **6** (suppl 2): 62–83.
25 Dixon W, Hyrich K, Warson K, Silman A, Symmons D. Serious infection rates in patients receiving biologic therapy in the United Kingdom: results from the BSR biologics register (BSRBR). *BSR Biologics Register Newsletter* 2006; March 2006: 9–10.
26 Keane J, Gershon S, Wise R, Mirabile-Levens E, Kasznica J, Schweiterman W *et al.* Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *New Engl J Med* 2001; **345**: 1098–104.
27 Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Breban M *et al.* Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy. *Arthritis Rheum* 2009; **60**: 1884–94.
28 British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing *Mycobacterium tuberculosis* infection and disease in patients due to start anti-TNFα treatment. *Thorax* 2005; **60**: 800–5.
29 Hutton MD, Cauthen GM, Bloch AB. Results of a 29-state survey of tuberculosis in nursing homes and correctional facilities. *Public Health Reports* 1993; **108**: 305–314.
30 Nisar M, Williams C, Ashby D, Davies P. Tuberculin testing in residential homes for the elderly. *Thorax* 1993; **48**: 1257–60.
31 Stead W. Tuberculosis among elderly persons: an outbreak in a nursing home. *Annals Intern Med* 1981; **94**: 606–10.
32 Office for National Statistics, UK, 2001. www.statistics.gov.uk
33 Prevention and control of tuberculosis in facilities providing long term care to the elderly. Recommendations of the advisory committee for elimination of tuberculosis. *MMWR Weekly Rep* 1990; **39** (RR-10): 7–20.
34 Khan K, Wang J, Marras T. Non-tuberculous mycobacterial sensitization in the United States:

https://doi.org/10.1017/S0959259810000110 Published online by Cambridge University Press

national trends over three decades. *Am J Resp Crit Care Med* 2007; **176**: 306–13.
35 Perez-Guzman C, Vargas M, Torres-Cruz A, Villareal-Velarde H. Does aging modify pulmonary tuberculosis? *Chest* 1999; **116**: 961–67.
36 Rocha M, Pereira S, Barros H, Seabra J. Does pulmonary tuberculosis change with ageing? *Int J Tuberculosis Lung Dis* 1997; **1**: 147–51.
37 Perez-Guzman C, Torres-Cruz A, Villareal-Velarde H, Vargas M. Progressive age-related changes in pulmonary tuberculosis images and the effect of diabetes. *Am J Resp Crit Care Med* 2000; **162**: 1738–40.
38 Geng E, Kreiswirth B, Burzynski J, Schluger N. Clinical and radiographic correlates of primary and reactivation tuberculosis. A molecular epidemiological study. *JAMA* 2005; **293**: 2740–45.
39 Greenaway C, Menzies D, Fanning A, Grewal R, Yuan L, Fitzgerald J. Delay in diagnosis among hospitalized patients with active tuberculosis – predictors and outcomes. *Am J Resp Crit Care Med* 2002; **165**: 927–33.
40 Wallace R, Kammerer S, Iademarco M, Althomsons S, Winston C, Navin T. Increasing proportions of advanced pulmonary tuberculosis reported in the United States: are delays in diagnosis on the rise? *Am J Resp Crit Care Med* 2009; **180**: 1016–22.
41 McNicol MW. Clinical features and management. In Brewis R, Gibson G, Geddes D (eds). *Respiratory Medicine*. 1st edn. London: Balliere Tindall, 1990.
42 Brown M, Varia H, Bassett P, Davidson R, Wall R, Pasvel G. Prospective study of sputum induction, gastric washing, and bronchoalveolar lavage for the diagnosis of pulmonary tuberculosis in patients who are unable to expectorate. *Clin Infect Dis* 2007; **44**: 1415–20.
43 Saglam L, Akgun M, Aktas E. Usefulness of induced sputum and fibre-optic bronchoscopy specimens in the first diagnosis of pulmonary tuberculosis. *J Int Med Res* 2005; **33**: 260–65.
44 Al Zahrani K, Al Jahdali H, Poirier L, Rene P, Gennaro M, Menzies D. Accuracy and utility of commercially available amplification and serologic tests for the diagnosis of minimal pulmonary tuberculosis. *Am J Resp Crit Care Med* 2000; **162**: 1323–29.
45 Noordhoek G, Kolk A, Bjune G, Catty D, Dale J, Fine P *et al.* Sensitivity and specificity of PCR for detection of *Mycobacterium tuberculosis*: a blind comparison study among seven laboratories. *J Clin Microbiol* 1994; **32**: 277–84.
46 Barnard M, Albert H, Coetzee G, O'Brien R, Bosman M. Rapid molecular screening for multidrug resistant tuberculosis in a high volume public health laboratory in South Africa. *Am J Resp Crit Care Med* 2008; **177**: 787–92.
47 Ling D, Zwerling A, Pai M. Genotype MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis. *Eur Resp J* 2008; **32**: 1165–74.
48 The Mantoux test. Administration, reading and interpretation. NHS: Department of Health Publications. Available at: http://www.immunisation.nhs.uk/Files/mantouxtest.pdf (accessed 18 March).
49 Mancusco J, Tobler S, Keep L. Pseudoepidemics of tuberculin skin test conversions in the US army after recent deployments. *Am J Resp Crit Care Med* 2008; **177**: 1285–89.
50 Chan-Yeung M, Cheung A, Dai D. Prevalence and determinants of positive tuberculin reactions in residents of old age homes in Hong Kong. *Int J Tuberculosis Lung Dis* 2006; **10**: 892–98.
51 Van Den Brande P, Demedts M. Four-stage tuberculin testing in elderly subjects induces age-dependent progressive boosting. *Chest* 1992; **101**: 447–50.
52 Mori T, Sakatani M, Yamagishi F, Takashima T, Kawabe Y, Nagao K *et al.* Specific detection of tuberculosis infection: an interferon gamma-based assay using new antigens. *Am J Resp Crit Care Med* 2004; **170**: 59–64.
53 Kobashi Y, Sugin T, Shimuza H, Ohue Y, Mouri K, Obase Y *et al.* Clinical evaluation of the T.spot.TB test for patients with indeterminate results on the QuantiFERON TB-2G test. *Intern Med* 2009; **48**: 137–42.
54 Menzies D, Madhukar P, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. *Annals Intern Med* 2007; **146**: 340–54.
55 Kobashi Y, Obase Y, Fukuda M, Yoshida K, Miyashita N, Oka M. Clinical re-evaluation of the Quantiferon TB-2G test as a diagnostic method for differentiating active tuberculosis from non-tuberculous mycobacteriosis. *Clin Infect Dis* 2006; **43**: 1540–46.
56 Dosanjh D, Hinks T, Innes J, Deeks J, Pasvol G, Hackforth S *et al.* Improved diagnostic evaluation of suspected tuberculosis. *Annals Intern Med* 2008; **148**: 325–36.
57 Arend S, Thijsen S, Leyten E, Bouwman J, Franken W, Koster B *et al.* Comparison of two interferon-γ assays and tuberculin skin test for tracing tuberculosis contacts. *Am J Resp Crit Care Med* 2007; **175**: 618–27.
58 Mazurek G, LaBue P, Daley C. Comparison of a whole blood interferon-gamma assay with tuberculin skin testing for detecting latent

https://doi.org/10.1017/S0959259810000110 Published online by Cambridge University Press

Mycobacterium tuberculosis infection. *JAMA* 2001; **286**: 1740–47.
59 Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-γ assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis*. *Am J Resp Crit Care Med* 2008; **177**: 1164–70.
60 Aiken A, Hill P, Fox A, McAdam K, Jackson-Sillah D, Lugos M *et al.* Reversion of the ELISPOT test after treatment in Gambian tuberculosis cases. *BMC Infect Dis* 2006; **6**: 66.
61 Chee C, KhinMar K, Gan S, Barkham M, Pushparani M, Wang Y. Latent tuberculosis infection treatment and T-cell responses to *Mycobacterium tuberculosis*. *Am J Resp Crit Care Med* 2007; **175**: 282–87.
62 Nahid P, Pai M, Hopewell P. Advances in the diagnosis and treatment of tuberculosis. *Proc Am Thoracic Soc* 2006; **3**: 103–10.
63 Rao S, Mookerjee A, Obasanjo O, Chaisson R. Errors in the treatment of tuberculosis in Baltimore. *Chest* 2000; **117**: 734–37.
64 David H. Probability distribution of drug-resistant mutants in unselected populations of *Mycobacterium tuberculosis*. *Appl Microbiol* 1970; **20**: 810–14.
65 Billington O, McHugh T, Gillespie S. Physiological cost of rifampin resistance induced *in vitro* in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 1999; **43**: 1866–69.
66 Mahmoudi A, Iseman M. Pitfalls in the care of patients with tuberculosis: common errors and their association with the acquisition of drug resistance. *JAMA* 1993; **270**: 65–68.
67 Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Resp Crit Care Med* 2003; **167**: 1472–77.
68 Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *Eur Resp J* 1995; **9**: 2026–30.
69 Fernandez-Villar A, Sopena B, Fernandez-Villar J, Vazquez-Gallardo R, Ulloa F, Leiro V *et al.* The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. *Int J Tuberculosis Lung Dis* 2004; **8**: 1499–505.
70 Chang K, Leung C, Yew W, Tam C. Standard anti-tuberculous treatment and hepatotoxicity: do dosing schedules matter? *Eur Resp J* 2007; **29**: 347–51.
71 Saukkonen J, Cohn D, Jasmer R, Schenker S, Jereb J, Nolan C *et al.* An official ATS statement: hepatotoxicity of antituberculous therapy. *Am J Resp Crit Care Med* 2006; **174**: 935–52.
72 Farah F, Taylor W, Rawlins M, James O. Hepatic drug acetylation and oxidation: effects of aging in man. *Br Med J* 1977; **2**: 155–56.
73 McIlleron H, Hackforth S, Wash P, Burger A, Norman J, Folb P *et al.* Determinants of rifampin, isoniazid, pyrazinamide, and ethambutol pharmacokinetics in a cohort of tuberculosis patients. *Antimicrob Agents Chemother* 2006; **50**: 1170–77.
74 Low S, Ang L, Cutter J, James L, Chee C, Wang Y *et al.* Mortality among tuberculosis patients on treatment in Singapore. *Int J Tuberculosis Lung Dis* 2009; **13**: 328–34.
75 Rao V, Iademarco E, Fraser V, Kollef M. The impact of comorbidity on mortality following in-hospital diagnosis of tuberculosis. *Chest* 1998; **114**: 1244–52.
76 Pablos Mendez A, Sterling T, Frieden T. The relationship between delayed or incomplete treatment and all-cause mortality in patients with tuberculosis. *JAMA* 1996; **276**: 1223–28.
77 Dooley K, Tang T, Golub J, Dorman S, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. *Am J Trop Med Hygiene* 2009; **80**: 634–39.
78 Falk A, Fuchs G. Prophylaxis with isoniazid in inactive tuberculosis. *Chest* 1978; **73**: 44–48.
79 Egsmose T, Ang'awa J, Pott S. The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. *Bulletin World Health Org* 1965; **33**: 419–33.
80 Girling D, Chan S. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Resp Dis* 1992; **145**: 36–41.
81 Lee A, Mennone J, Jones R, Paul W. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *Int J Tuberculosis Lung Dis* 2002; **6**: 995–1000.
82 Aziz H, Shubair M, DeBari V, Ismail M, Khan M. Assessment of age-related isoniazid hepatotoxicity during treatment of latent tuberculosis infection. *Curr Med Res Opin* 2006; **22**: 217–21.
83 Sorresso D, Mehta J, Harvill L, Bentley S. Underutilization of isoniazid chemoprophylaxis in tuberculosis contacts 50 years of age and older. *Chest* 1995; **108**: 706–11.
84 Shieh F, Snyder G, Horsburgh R, Bernardo J, Murphy C, Saukkonen J. Predicting non-completion of treatment for latent tuberculosis

https://doi.org/10.1017/S0959259810000110 Published online by Cambridge University Press

infection. *Am J Resp Crit Care Med* 2006; **174**: 717–21.
85 Balcells M, Thomas S, Godfrey-Faussett P, Grant A. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerging Infect Dis* 2006; **12**: 744–51.
86 American Thoracic-Society. Targeted tuberculin skin testing and treatment of latent tuberculosis infection. *Am J Resp Crit Care Med* 2000; **161**: S221–47.
87 Zevallos M, Justman J. Tuberculosis in the elderly. *Clinics Geriatr Med* 2003; **19**: 121–38.
88 Thrupp L, Bradley S, Smith P, Simor A, Gantz N, Crossley K *et al.* Tuberculosis prevention and control in long-term-care facilities for older adults. *Infection Control Hosp Epidemiol* 2004; **25**: 1097–108.
89 Trial of BCG vaccines in south India for tuberculosis prevention: first report. *Bulletin World Health Org* 1979; **57**: 819–27.
90 Sterne J, Rodrigues L, Guedes I. Does the efficacy of BCG decline with time since vaccination? *Int J Tuberculosis Lung Dis* 1998; **2**: 200–7.
91 Leung C, Tam C, Chan S, Chan-Yeung M, Chan C, Chang K. Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. *Int J Tuberculosis Lung Dis* 2001; **5**: 717–23.
92 Jindani A, Dore C, Mitchison D. Bactericidal and sterilizing activities of antituberculosis drugs during the first 14 days. *Am J Resp Crit Care Med* 2003; **167**: 1348–54.
93 Bailey W, Gerald L, Kimerling M, Redden D, Brook N, Bruce F *et al.* Predictive model to identify positive tuberculosis skin test results during contact investigations. *JAMA* 2002; **287**: 996–1002.
94 Reichler M, Reves R, Bur S, Thompson V, Mangura B, Ford J *et al.* Evaluation of investigations conducted to detect and prevent transmission of tuberculosis. *JAMA* 2002; **287**: 991–95.
95 Meredith S, Watson J, Citron K, Cockcroft A, Darbyshire J. Are healthcare workers in England and Wales at increased risk of tuberculosis? *Br Med J* 1996; **313**: 522–25.
96 Kline S, Hedemark L, Davies S. Outbreak of tuberculosis among regular patrons of a neighborhood bar. *New Engl J Med* 1995; **333**: 222–27.
97 A strategic plan for the elimination of tuberculosis in the United States. *MMWR Suppl* 1989; **38** (S–3): 1–25.

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