TUBERCULOSIS

Nick Marchant

Office of Health Economics
12 Whitehall London SW1A 2DY

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Office of Health Economics

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- collect and analyse health and health care data from the UK and other countries;
- disseminate the results of this work and stimulate discussion of them and their policy implications.

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CONTENTS

1 INTRODUCTION

The first Office of Health Economics (OHE) disease state booklet, written in 1962, was entitled 'Progress against Tuberculosis' and was published at a time of great optimism among health care professionals involved in the battle against tuberculosis (TB). Effective anti-tuberculosis medications had recently been developed and were in widespread use. The booklet noted that '...the use of these drugs, combined with traditional methods of treatment, had opened up the possibility of the final defeat of TB in Britain within 15 years'.

Thirty-five years on that optimism appears misplaced. Approximately 6,000 TB notifications and 600 deaths are still reported annually in the UK. In addition, the continual decline in TB-associated morbidity and mortality that had occurred throughout this century (except during the war-effected 1940s) has not been apparent during the current decade. The 1990s have been a period when TB notifications have levelled out and, indeed, have even increased.

The global problem is even more acute. The World Health Organisation (WHO) estimated the incidence and mortality of TB in 1990 to be 7.5 million and 2.5 million, respectively (Dolin et al, 1994). These figures are predicted to rise to 10.2 million and 3.5 million, respectively, by the year 2000. TB is now the single largest infectious disease killer in the world.

This paper sets out what is currently known about TB and asks why a disease which we thought we had the capability to eradicate three decades ago is not only still with us but causing morbidity and mortality on such a scale that the WHO declared TB a global emergency in 1993. The clinical aspects of TB are presented in Chapter Two. Chapter Three covers the epidemiology of the disease, from both a global and a UK perspective. Available diagnostic procedures are outlined in Chapter Four. Prevention and treatment techniques are discussed in Chapters Five and Six, respectively. Economic issues relevant to TB are considered in Chapter Seven. These include the cost implications of TB to the UK National Health Service, and the appropriateness of continuing with a non-selective teenage BCG vaccination programme in the United Kingdom. Conclusions that can be drawn from the available data, with particular emphasis on implications for the UK, are discussed in Chapter Eight.

2 WHAT IS TUBERCULOSIS?

TB is a disease with a long history. Writings indicate that it was well known to the ancient Greeks, Indians, Chinese and Persians. Bone TB has been identified in Stone Age skeletons and Egyptian mummies (Bignall, 1986). Hippocrates, writing in the 5th century BC, used the term 'phthisis' for wasting disease. 'Pulmonary phthisis' was later used for labelling wasting with pulmonary symptoms (Styblo, 1986).

Although the disease had been known about for many centuries it was not until 1882 that Robert Koch first identified the tubercle bacillus. The term TB is now the general name for a group of diseases caused by the bacterium *Mycobacterium tuberculosis*. TB most commonly affects the lungs, causing a condition known as pulmonary TB, but can affect almost any part of the body. *Mycobacterium tuberculosis* is a contagious infection carried on droplets in the air, known as droplet nuclei – a finding first made by Flugge in 1897 (Flugge, 1897). An infected person can spread TB bacilli into the air by coughing, sneezing or even talking. People inhaling these bacilli may themselves become infected. Transmission can also occur by inoculation or ingestion.

2.1 Nature of the disease

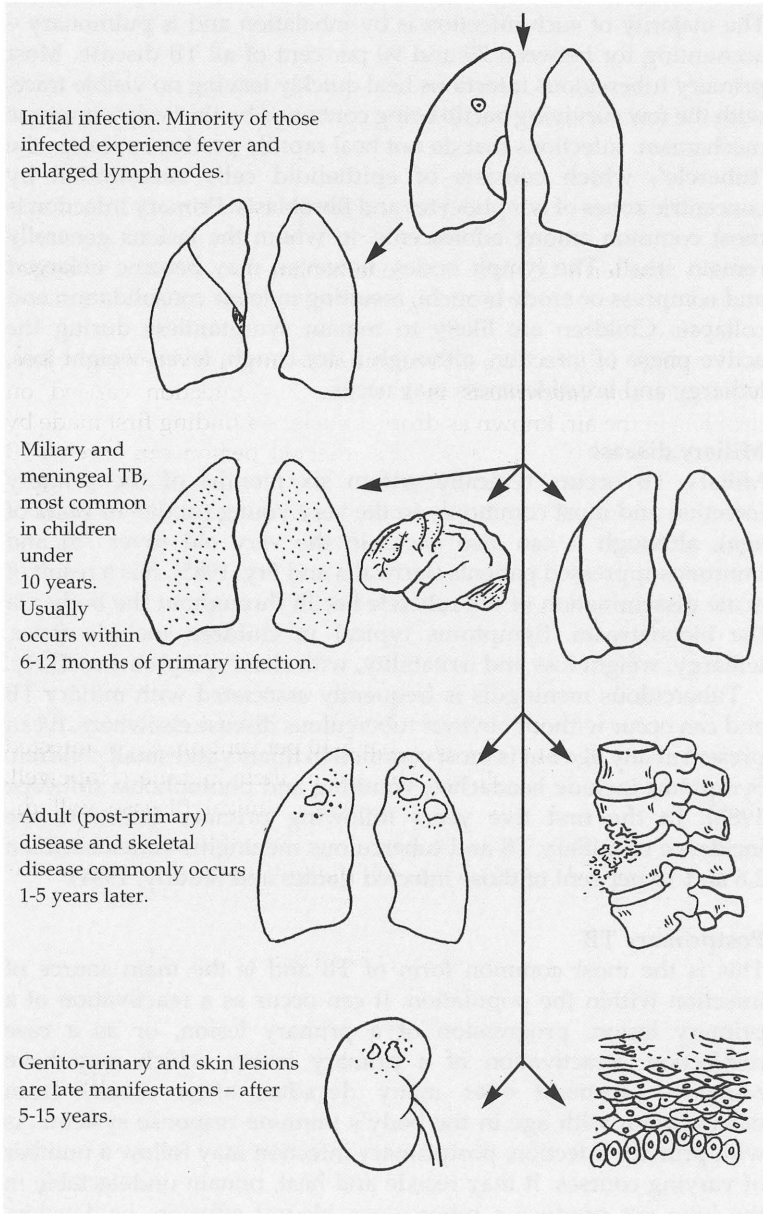
The majority of people who are infected with the tubercle bacillus never become infectious or develop symptomatic disease as their own immune system is able to 'wall off' the bacillus, causing it to remain dormant. It is estimated that 5-10 per cent of people infected with TB will develop clinical disease in their lifetime (Hopewell, 1986) and 1-5 per cent of people with clinical disease will die (Cullinan et al, 1991; Humphries et al, 1984). Infected people may develop active TB at any stage throughout their life although it is more likely to occur closer to the time of infection. However, if the immune system weakens, as a result of diabetes, cancer or AIDS for example, then the probability of active TB developing increases.

Tuberculous infection describes a state in which the tubercle bacillus is present within the body without there being any evidence of disease. Tuberculous disease describes a state in which at least one organ of the body is shown by diagnostic procedures to be diseased.

2.2 Forms of the disease and their clinical presentation

TB disease can take many forms which generally conform to a 'sequential timetable' following the initial infection (Wallgren, 1948) (see Figure 1).

Figure 1 **Natural history of untreated primary tuberculosis**



Source: Adapted from Seaton et al, 1989.

Primary TB

Initial infection with the tubercle bacillus is known as primary TB. The majority of such infection is by inhalation and is pulmonary – accounting for between 70 and 90 per cent of all TB disease. Most primary tuberculous infections heal quickly leaving no visible trace, with the few surviving bacilli being contained by the body's immune mechanism. Infections that do not heal rapidly produce a lesion, the 'tubercle', which consists of epithelioid cells surrounded by concentric zones of lymphocytes and fibroblasts. Primary infection is most common among adolescents, in whom the lesions generally remain small. The lymph nodes, however, may become enlarged and compress or erode bronchi, resulting in lobar consolidation and collapse. Children are likely to remain symptomless during the active phase of infection, although a dry cough, fever, weight loss, lethargy and breathlessness may occur.

Miliary disease

Miliary TB occurs typically within six months of the primary infection and most commonly in the very young (under 10 years of age), although it can also occur in the very old (over 75) and immunosuppressed patients (Jariwalla and Fry, 1985). It is a result of acute dissemination of the tubercle bacilli throughout the body via the bloodstream. Symptoms typical in children include fever, lethargy, weight loss and irritability, with chest symptoms unlikely.

Tuberculous meningitis is frequently associated with miliary TB and can occur without obvious tuberculous disease elsewhere. It can present at any age but is most common in infants and small children. Symptoms include headaches, vomiting and photophobia (Meyers, 1982). In the first five years following primary infection, the incidence of miliary TB and tuberculous meningitis varies between 2.6 and 16 per cent of those infected (James and Studdy, 1981).

Postprimary TB

This is the most common form of TB and is the main source of infection within the population. It can occur as a reactivation of a primary lesion, progression of a primary lesion, or as a case reinfection. Reactivation of a primary lesion, which may have remained dormant over many decades, often results from deterioration with age in the body's immune response system. As with primary infection, postprimary infection may follow a number of varying courses. It may recede and heal, remain undetectable in the lung yet produce a tuberculous pleural effusion, or develop. Progression, which can occur at varying rates, is at first localised but

will later spread as the numbers of bacilli increase. Disease can spread to almost any part of the body. Symptoms associated with this form of TB are often non-specific and may include tiredness, weight loss, anorexia, night sweats, indigestion, chest pains and a persistent cough. Skeletal tuberculous lesions, especially of the spine, occur some 1-5 years after the primary infection. Genito-urinary TB commonly develops 5-15 years after the primary infection.

The development of clinical TB following infection during adolescence was studied in a Medical Research Council TB vaccines trial (1956, 1959, 1963, 1972). The 1972 report details the 15-year follow-up results of 54,239 participants who presented themselves during 1950-52 for the first examination. All participants were initially free from active TB and from known contact with the disease at home and nearly all were aged 14 to $15^1/_2$ years on entry. All participants were tuberculin tested. Those with negative results (32,282) were vaccinated with either BCG (13,598) or vole bacillus vaccine (5,817), or left unvaccinated (12,867), based on a system of randomisation (see Table 8 in section 5.2 of this report). 248 cases of TB developed in the tuberculin-negative unvaccinated group, 67 per cent of which were of the non-miliary pulmonary form. Approximately two-thirds of all TB cases occurred in the first five years after trial entry.

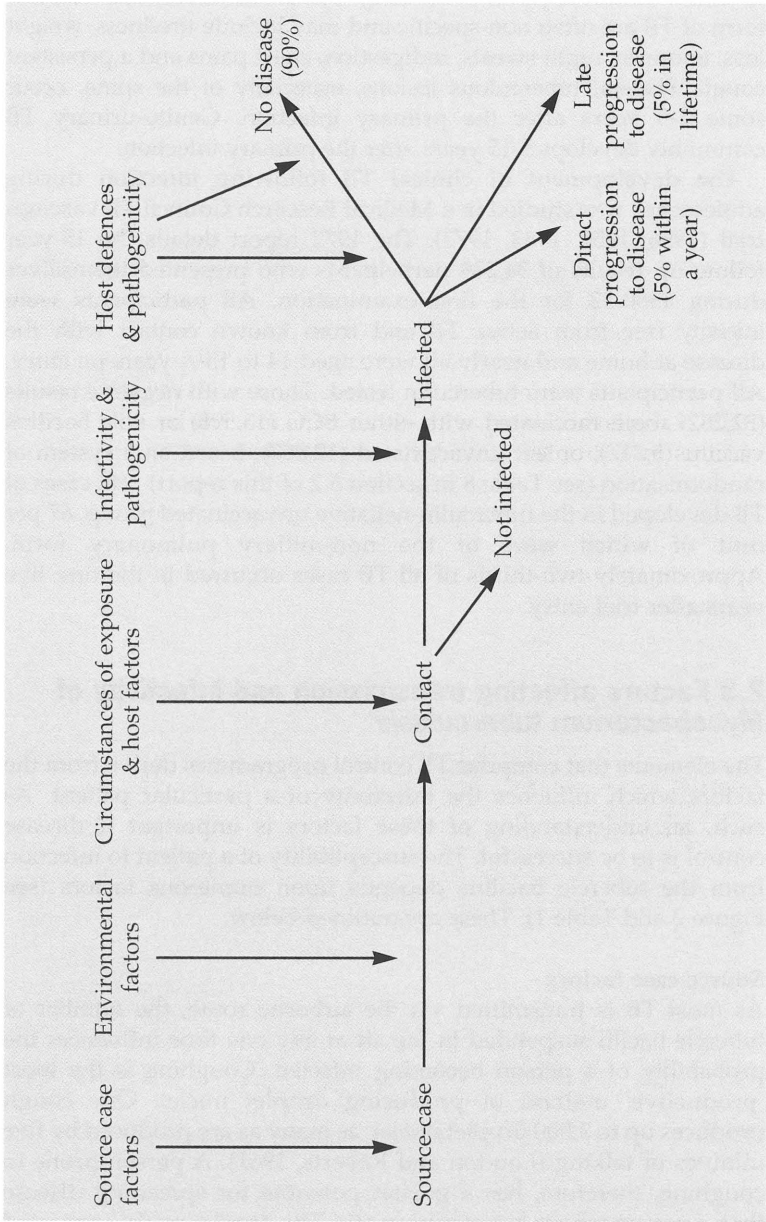
2.3 Factors affecting transmission and infectivity of *Mycobacterium tuberculosis*

The elements that comprise TB control programmes derive from the factors which influence the infectivity of a particular patient. As such, an understanding of these factors is important if disease control is to be successful. The susceptibility of a patient to infection from the tubercle bacillus depends upon numerous factors (see Figure 2 and Table 1). These are outlined below.

Source case factors

As most TB is transmitted via the airborne route, the number of tubercle bacilli suspended in the air at any one time influences the probability of a person becoming infected. Coughing is the most 'productive' method of producing droplet nuclei. One cough produces up to 3,500 droplet nuclei, as many as are produced by five minutes of talking (Loudon and Roberts, 1967). A person prone to coughing, therefore, has a greater potential for spreading disease than a person who is less symptomatic. The droplet nuclei generated by coughing, or spitting, sneezing, talking etc., can remain

Figure 2 **Steps in the pathogenesis of TB**



Source: Adapted from Hopewell, 1986.

suspended in the air for several hours (Wells, 1934). Differences in infectiousness between patients were demonstrated in a study by Riley et al (1962). A research ward occupied by a succession of smear-positive patients had its air vented through exhaust ducts past guinea-pig colonies before passing to the outside. Matching the patterns of bacilli from infected guinea-pigs with that of patients in the ward indicated that of 61 untreated patients who passed through the ward, only eight transmitted the disease to the guinea pigs.

The physical and chemical characteristics of the sputum, in addition to the frequency of forced expiratory manoeuvres, may also influence infectiousness. Watery sputum can easily be broken down into small droplets with a high water content which evaporate quicker than more viscous sputum which has a lower water content (Riley et al, 1959). The significance of the size of the infecting particle was demonstrated in a series of experiments by Wells et al (1948, 1955). Rabbits inhaling two to three bovine tubercle bacilli as a single bacillus in a droplet nucleus contracted more pulmonary TB than

Table 1 **Factors influencing transmission and infectivity of *Mycobacterium tuberculosis***

Source case factors
Production of aerosols of respiratory secretions
– Severity of coughing
– Frequency of other forced expiratory manoeuvres
Population of organisms residing in the lungs
Effects of chemotherapy
Environmental factors
Pattern and volume of air recirculation
Effects of ultraviolet light
Circumstances of the exposure
Intensity and duration of exposure
Variations in infectivity and pathogenicity
Natural variations presumably related to biochemical constituents of the organism
Acquired variations associated with resistance to isoniazid
New host factors
Integrity and effectiveness of both immunologic and nonimmunologic host defences
Protection provided by previous infection with *Mycobacterium tuberculosis*
Protection provided by infection with other mycobacteria (including BCG)

Source: Hopewell, 1986.

rabbits inhaling 10,000 bacilli in a larger particle. This is because the smaller particles are deposited on the alveolar surface of the lungs whereas the larger particles are deposited in airways from where they are removed from the lung by the mucociliary clearance system. Nearly all tubercle bacilli inhaled as single organisms are deposited on alveoli (Ratcliffe and Palladino, 1953).

Infectiousness is also influenced by the number of bacilli contained within the lungs of the source case. The number of bacilli contained within tuberculous lesions varies greatly depending on the morphology of the lesion. Solid nodular lesions contain up to 10^4 bacilli, whilst up to 10^9 bacilli may be harboured in a cavitary lesion (Canetti, 1965). Patients with multiple cavitary lesions therefore have the potential to be highly infectious.

The sputum from patients receiving effective chemotherapy is less infectious than that from other smear-positive patients. Chemotherapy reduces infectiousness in several ways. Firstly, the direct effect of the medicines used for treatment is to reduce the number of bacilli contained in the lungs. Hobby et al (1974) reported a 99 per cent decrease in the number of bacilli per ml of sputum after an average 15.6 days of multiple drug therapy. Secondly, chemotherapy alters the composition of the droplets containing the bacilli which makes the bacilli less able to survive in the air or in the lungs of a new host. Treatment by chemotherapy also reduces the frequency of coughing experienced by a patient, thus decreasing the number of droplet nuclei expelled into the air (Loudon and Spohn, 1969). It is estimated that chemotherapy reduces the infectiousness of a patient by 99.9 per cent (Hopewell, 1986). Once effective chemotherapy has begun, a patient is very unlikely to transmit the bacilli to an uninfected host.

Environmental factors

The infectivity of a droplet nucleus under normal conditions of temperature and humidity indoors is influenced by the presence of ultraviolet light and the existence of a filtering or venting system. Tubercle bacilli are killed on exposure to ultraviolet irradiation (Rich, 1944). As such, ultraviolet lights are a useful tool for combating transmission of *Mycobacterium tuberculosis* in places where patients with untreated TB may be present, such as hospital waiting rooms. Transmission of *Mycobacterium tuberculosis* is made easier by the lack of a system which effectively vents or filters the air. A recirculating venting system, for example, increases the likelihood of one infective person spreading tubercle bacilli to other new hosts. The potential hazards of such an air circulation system were clearly

demonstrated on board a US naval vessel. One TB infected sailor transmitted infections to 53 of 60 sailors in his sleeping compartment and 43 of 81 sailors in an adjacent compartment connected to the same ventilation system (Houk et al, 1968). It is now common practice in hospitals not to recirculate the air from a patient's room to other parts of the hospital. The high number of infections that occurred on board the US naval ship also serves to demonstrate that the likelihood of transmission is greater when there is a high concentration of droplet nuclei in the air and when the length of exposure to these droplets is prolonged.

Variations in infectivity and pathogenicity

The ability of *Mycobacterium tuberculosis* to produce infection in a new host (pathogenicity), once it is established within the body, varies between organisms. Tests on tubercle bacilli strains taken from Indian and British patients indicated that the British strains were more pathogenic than the Indian ones (Mitchison et al, 1960; Gangadharam et al, 1963). The existence of sulfolipids[1], for example, effects pathogenicity (Youmans, 1979). The impact of drug-resistant strains of *Mycobacterium tuberculosis* on infectivity and pathogenicity is contentious. Riley et al (1962) estimated drug-resistant strains to be only 28 per cent as infectious as fully susceptible strains. These results support previous studies suggesting that drug-resistant strains have a lower level of pathogenicity (Middlebrook et al, 1953; Cohn et al, 1954). More recent studies, however, indicate that some drug-resistant strains of the tubercle bacillus have levels of infectiousness and pathogenicity similar to other fully susceptible strains (Steiner et al, 1970; Bonforte et al, 1968).

Host defences

There are two natural defence mechanisms that a person has to prevent infection with *Mycobacterium tuberculosis*. A non-immunologic defence mechanism involves the blocking of particles entering the lungs by a system of 'barriers' contained in the nose, which filter out particles above a certain size. The immunologic response to tubercle bacilli reaching the alveoli of the lungs involves the production of polymorphs[2] and macrophages[3] which ingest

1 Class of lipids in which fatty acids are combined with sulphuric acid and a nitrogeneous base.

2 Colloquial term for any of the fully developed, segmented cells of the granulocytic series.

3 A cell with a single nucleus capable of ingesting particulate matter.

some of the bacilli. Within several weeks, the macrophages predominate and crowd together to form epithelioid[4] cells. These cells consolidate to form the tubercle lesion, which is surrounded by lymphocytes[5]. An area of caseous necrosis[6] can appear in the centre of the lesion, which may later calcify. The patient will develop hypersensitivity to tubercular protein within eight weeks (Flenley, G). T lymphocytes are sensitised to release cytokines[7] which activate macrophages, so increasing their effectiveness as bacterial killers. This immunologic response to initial infection generally results in most of the bacilli being either killed or 'walled off' by tissue reaction.

Immunologic resistance to new infection is greater amongst people who have previously been infected. The BCG vaccine for combating infection is based on this finding and as such contains a strain of the tubercle bacillus. It is unclear, however, what level of protection a patient receives from previous infection and indeed whether new exogenous infection or reactivation of latent organisms is more likely to result in clinical TB. It appears likely that the majority of re-infecting organisms are killed speedily, quicker than is the case for primary infection, but some survive to cause cases of clinical TB (Snider et al, 1984). Reinfection is more likely in populations which have a high TB prevalence, as was previously the case in Eskimo communities (Johnson, 1973).

Predisposing factors to primary infection and the reactivation of tubercle lesions

As discussed earlier, reactivation may occur at any time after the initial infection. Reinfection occurs as the result of a decline in the performance of a host's defence mechanism. Factors which may play a part in this decline and also contribute to the risk of initial infection include:

- Presence of human-immunodeficiency virus (HIV). Diseases that debilitate a patient's immune system encourage reactivation. Of such diseases, HIV has had most impact on increasing TB numbers

4 Resembling the epithelium – the covering of internal and external surfaces of the body.

5 Mononuclear cells, incapable of ingesting particulate matter, found in the blood, lymph and lymphoid tissues.

6 Death of a portion of tissue in which structures or tissues are changed into a cheesy mass.

7 General term for nonantibody proteins released by one cell population on contact with specific antigen.

(see section 3.1). HIV infection causes CD4+ lymphocytes to decline in number and function, resulting in the immune system being less able to ward off the growth and spread of *Mycobacterium tuberculosis* (Helbert et al, 1990). It is estimated that an HIV-infected individual has at least a 10-times increased risk, and probably much higher, of developing TB compared to a non-infected individual (WHO, 1996a; O'Brien, 1994).

- Presence of other diseases. Other illnesses which increase a person's susceptibility to infection include diabetes mellitus (Hendy et al, 1983), illness leading to gastrectomy[8] (Snider, 1985) and leukaemia. Use of steroids and other immunosuppressant medicines for the treatment of disease may also cause reactivation (Sahn et al, 1976).
- Workers exposed to silica, which causes pulmonary silicosis, have an increased chance of developing TB (Snider, 1978). Silica reduces a person's resistance to infection through a toxic effect on pulmonary macrophages (Allison et al, 1966). Coalminers, quarry workers and masons are workers more likely to be exposed to silica. Increased prevalence has also been reported amongst health service workers due to their greater risk of exposure to the tubercle bacilli. Meredith et al (1996) estimated the relative risk, adjusted for ethnic group, age, sex and socio-economic status, for all health care workers compared with workers in other occupations to be 2.4.
- Poor housing conditions. Overcrowding provides greater potential for the spread of infection (Mangatani et al, 1995; Bhatti et al, 1995; Capewell et al, 1986). An analysis of standardised annual TB mortality rates for the 403 local authority districts in England and Wales between 1982 and 1992 demonstrated a strong association between TB mortality and overcrowding at the household level (Elender et al, 1998). The significance of overcrowding at the household level, as opposed to the district level, suggests that prolonged contact is required for disease transmission.
- Malnutrition. There is much anecdotal and epidemiological evidence supporting the view that poor nutrition predisposes to TB. One such example was the sudden increase in TB mortality that occurred among French prisoners of war in Germany after they stopped receiving Red Cross food parcels in 1944 (Seaton et al, 1989).
- Smoking and alcohol intake. The damaging effects that smoking and alcohol intake have on a host's defences (Smith et al, 1976) have been demonstrated in a number of studies. Doll et al (1976) and

8 Removal of all or part of the stomach.

Kahn (1966) reported a link between smoking levels and increased mortality from pulmonary TB. A link has also been reported between alcohol intake and TB morbidity (Brown et al, 1961).

The historical trends in the UK, which have demonstrated a greater prevalence of TB infection among the lower social classes (Spence et al, 1993), reflect the greater exposure of the poorer sections of society to many of these factors. However, assigning relative importance to these predisposing factors is difficult as they are often interlinked.

3 EPIDEMIOLOGY

3.1 Global outlook

Estimates of the prevalence[9], incidence[10] and mortality of TB world-wide come principally from WHO sources. Historical data are limited but the growth of the global TB epidemic has heightened the need for greater reporting and consequently the WHO has been collecting case notification data since 1984 from all of its member states as well as other countries in order to assess the burden of disease and world-wide trends.

Morbidity

It is estimated that approximately one-third of the world's population – nearly two billion people – is infected with the tubercle bacilli (WHO, 1995). Nearly 90 per cent of cases occur in developing countries. Estimates of world-wide infection prevalence by region were carried out by the WHO for 1990 (see Table 2). Prevalence was highest in the Western Pacific region (43.8 per cent) and lowest in the East Mediterranean region (19.4 per cent). India and China are the countries with the highest number of prevalent TB cases, accounting for 30 and 17 per cent, respectively, of all prevalent cases in the world (Murray et al, 1996).

Table 2 **WHO estimates of world-wide prevalence of TB infection, 1990**

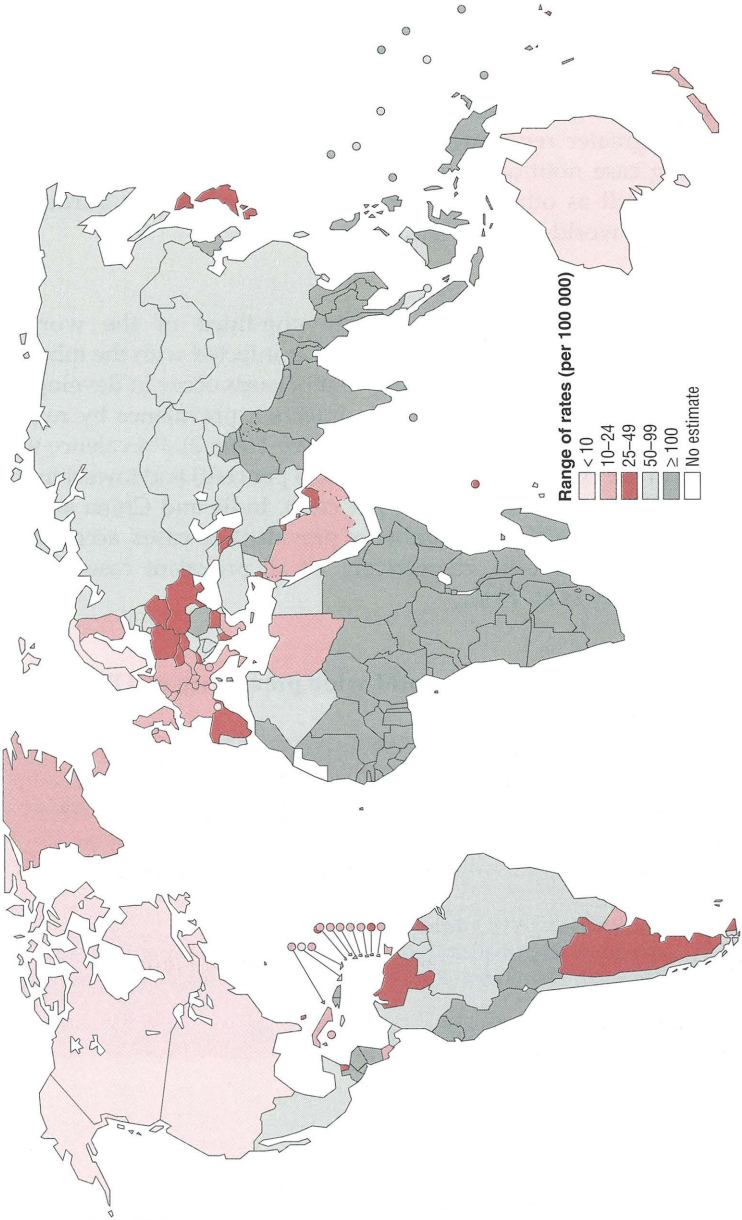
Region	*Africa*[a]	*Americas*[b]	*East Mediter-ranean*[a]	*Southeast Asia*[a]	*Western Pacific*[c]	*China*[a]	*Europe*[a] *& others*[d]
Prevalence (%)	33.8	25.9	19.4	34.3	43.8	33.7	31.6

Notes:
a) All countries in the WHO region.
b) All countries in the American region of WHO, except USA and Canada.
c) All countries in the Western Pacific region, except China, Japan, Australia and New Zealand.
d) USA, Canada, Japan, Australia and New Zealand.

Source: Adapted from Kumar et al, 1994.

9 Prevalence: total number of cases at any one time.
10 Incidence: total number of new cases occurring in one particular time period, usually one year.

Figure 3 **Estimated tuberculosis incidence rates, 1996**



Source: WHO Global Tuberculosis Programme, 1996b.

The most recent case notification data, detailing TB disease rates as opposed to TB infection rates, are for 1996 (WHO Global Tuberculosis Programme, 1998). The number of global cases notified in this year totalled 3,805,063, with Africa and South-East Asia experiencing the highest TB rates per 100,000 population (see Table 3). Notification rates fall a long way below incidence estimates, however, as detection and reporting of TB cases is often likely to be poor, particularly in the African region.

Table 3 **TB cases notified in the world, 1996**

WHO region	*Cases notified*	*Rate (per 100,000 population*)*	*% of total notifications*
Africa	675,938	110.5	18
Americas	242,157	30.7	6
Eastern Mediterranean	144,552	61.2	4
Europe	321,033	37.4	8
South-East Asia	1,481,017	101.6	39
Western Pacific	940,366	57.6	25
GLOBAL	3,805,063	65.3	100
*1997 population figures, source: WHO, 1998.			

Source: WHO Global Tuberculosis Programme, 1998.

Current and future TB incidence levels are estimated in a WHO study which based its findings on TB notification data, estimates of the annual risk of infection in particular countries, epidemiological and demographic factors (Dolin et al, 1994). The study estimated that there were 7,537,000 incident cases of TB globally in 1990 (See Table 4). Nearly five million of these cases (65 per cent) were reported in the South-East Asian and Western Pacific regions. Africa accounted for approximately one million cases, with the industrialised countries experiencing 196,000 cases. The areas where TB infection are most concentrated can be seen in Figure 3.

The authors estimate that 4.2 per cent (315,000) of all cases in 1990 were attributable to HIV infection. Their finding is based on current data which indicate that 5-10 per cent of people infected with both HIV and *Mycobacterium tuberculosis* will develop TB annually (Selwyn et al, 1989; Narain et al, 1992). This compares with less than 0.2 per cent of people infected with only *Mycobacterium tuberculosis.*

Incidence is forecast to rise to 10.2 million new cases annually by the year 2000, an increase of 36 per cent during the decade. Africa will bear the brunt of this increase, both in terms of actual cases (one

Table 4 **Estimated TB incidence and HIV-attributable TB cases in 1990 and 2000, by region**

Region	*1990*			*2000*		
	Total TB cases	*Rate[e]*	*HIV-attributed TB cases*	*Total TB cases*	*Rate[e]*	*HIV-attributed TB cases*
South-East Asia	3 106 000	237	66 000	3 952 000	247	571 000
Western Pacific[a]	1 839 000	136	19 000	2 255 000	144	68 000
Africa	992 000	191	194 000	2 079 000	293	604 000
Eastern Mediterranean	641 000	165	9 000	870 000	168	38 000
Americas[b]	569 000	127	20 000	645 000	120	97 000
Eastern Europe[c]	194 000	47	1 000	210 000	48	6 000
Industrialised countries[d]	196 000	23	6 000	211 000	24	26 000
Total	7 537 000	143	315 000 (4.2%)	10 222 000	163	1 410 000 (13.8%)

Notes:
a) Includes all countries of the Western Pacific Region of WHO, except Japan, Australia and New Zealand.
b) Includes all countries of the American Region of WHO, except USA and Canada.
c) Eastern European countries, and independent states of the former USSR.
d) Western European countries, USA, Canada, Japan, Australia and New Zealand.
e) Rate per 100,000 population.

Source: Dolin et al, 1994.

million to 2.1 million) and incidence rates (191 to 293 per 100,000 population). The HIV epidemic in sub-Saharan Africa will be the major single factor for this increase. Age specific incidence rates in South-East Asia and Central and South America are forecast to fall during the 10 year period to 2000, although the actual number of new cases will continue to rise because of population growth. The Western Pacific and Eastern Mediterranean regions will also experience relatively small increases in the number of new cases as a result of demographic factors. TB incidence rates in Eastern Europe are expected to rise gradually throughout the decade, after nearly 40 years of steady decline, due mainly to the impact of recent political, social and economic changes on health systems in the region.

Notification rates for some industrialised countries are predicted to worsen slightly, partly as a result of increasing migration of people from areas with higher incidence rates and partly as a result

of co-infection with HIV. The USA and Holland, for example, have recently reported an increase in the number of TB cases after a sustained period of decline (Raviglione et al, 1993). The projected increase in HIV infection in South-East Asia over the next ten years has implications for the UK, as more than 40 per cent of UK TB cases are of Indian subcontinent ethnic origin and there is significant continued contact between the ethnic communities in the UK and in the Indian subcontinent.

The number of new cases per year in Western Europe will rise also as a result of population growth. Of the additional 2.7 million cases per year predicted to occur in 2000 compared with 1990, 80 per cent will be a result of demographic factors, particularly population growth and the changing age structure, within countries. Epidemiological factors will account for the remaining 20 per cent, mainly due to rising incidence rates in sub-Saharan Africa as a result of the HIV epidemic.

The age profile of those people with TB is expected to alter slightly during the 10 years to 2000. In 1990 57 per cent of TB incidence occurred in people aged 35 or older. This figure is estimated to rise to 60 per cent by 2000, principally a result of demographic changes. Age-specific incidence rates will vary little over the period. There are, however, significant variations between regions in the age distributions of infected cases. In Africa 77 per cent of cases occur in people aged under 50, whereas in Europe approximately 80 per cent of infected cases are in people aged 50 or over (Kumar et al, 1994). These variations in age distribution have a significant impact on the number of TB cases in association with HIV infection. HIV infection globally is most frequent amongst young adults and as such has resulted in Africa having a high proportion of young adults who have co-infection with HIV and TB. In comparison, young adults in developed countries tend to have a low prevalence of TB infection and, therefore, the already low rates of HIV infection lead to only a small proportion of co-infection. TB rates in developed countries are higher amongst elderly people who have negligible HIV rates, also leading to small co-infection rates.

Mortality

As with incidence of morbidity, the vast majority of TB deaths will be experienced in South-East Asia, the Western Pacific and Africa (See Table 5). The annual number of world-wide deaths is forecast to increase 39 per cent from 2.53 million in 1990 to 3.51 million in 2000. The greatest single change during the decade is that the number of deaths in Africa will more than double to 823,000 each year.

Table 5 **Estimated total TB deaths in 1990 and 2000**

Region	*Deaths in 1990*		*Deaths in 2000*	
	Total	*Attributed to HIV*	*Total*	*Attributed to HIV*
South-East Asia	1 087 000	23 000	1 383 000	200 000
Western Pacific[a]	644 000	7 000	789 000	24 000
Africa	393 000	77 000	823 000	239 000
Eastern Mediterranean	249 000	4 000	338 000	15 000
Americas[b]	114 000	4 000	129 000	19 000
Eastern Europe[c]	29 000	<200	32 000	<900
Industrialised countries[d]	14 000	<500	15 000	2 000
Total	2 530 000	116 000	3 509 000	500 000

Notes:
a) Includes all countries of the Western Pacific Region of WHO, except Japan, Australia and New Zealand.
b) Includes all countries of the American Region of WHO, except USA and Canada.
c) Eastern European countries and independent states of the former USSR.
d) Western European countries, USA, Canada, Japan, Australia and New Zealand.

Source: Dolin et al, 1994.

Total incidence and deaths during 1990-1999

It is estimated that 88.2 million people world-wide will develop TB during the period 1990-1999 (Dolin et al, 1994). 35.1 million of these cases will be in South-East Asia, with Western Europe totalling 1.1 million cases during the decade. HIV-attributable cases will number 8.0 million world-wide. The number of people who will die from TB during this decade is estimated to total 30.0 million, with 2.9 million of these deaths being attributable to HIV infection. South-East Asia, Africa and the Middle East will collectively account for 21.2 million deaths.

The ratio of cumulative TB cases to cumulative TB deaths differs widely between regions, highlighting the varying success of countries in combating the disease. Africa and the Middle East has a ratio of 2.5:1, South-East Asia a ratio of 2.9:1, whereas the ratios for Western Europe and North America are 15.3:1 and 14.5:1 respectively.

3.2 UK outlook

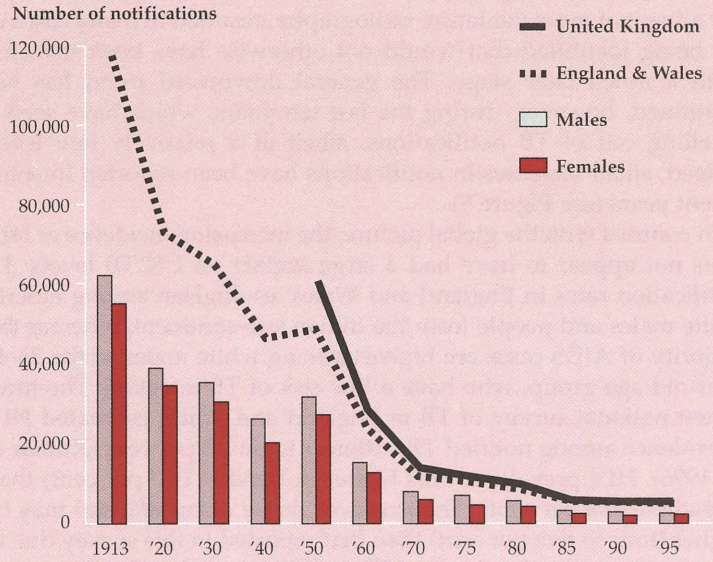
There are more extensive historical epidemiological data available on TB for the UK than for most other countries. Some information is available for as far back as 1850, although TB only became officially

notifiable in England and Wales in 1912. Since the beginning of the 20th century there has been a dramatic decline in both mortality and morbidity levels for TB within the UK.

Morbidity

UK morbidity data for the early part of this century are not totally reliable and Scotland and Northern Ireland did not record such data prior to World War II. It is also likely that notifications are considerably less than the actual number of cases, as people are often asymptomatic and so are unaware that they are infected. The problem of under reporting is still apparent today, although the actual level is not known. A 1992 retrospective survey of all patients

Figure 4 **TB notifications in the UK**



Notes:
a) Figures comprise only the formal notifications of new cases of TB. They exclude transfers between areas, in so far as they could be ascertained, duplicate notifications and a few cases brought to the notice of Medical Officers of Health otherwise than by formal notification under the regulations.
b) Breakdown of male and female notifications relates to England and Wales up to 1940 and to United Kingdom from 1950 onwards.

Sources: Annual reports of the Chief Medical Officer of the Ministry of Health.

aged 16 or more diagnosed as having TB, at two hospitals in East London over a five year period, estimated the level of undernotification to be 27 per cent (Sheldon et al, 1992); this was reduced to 7 per cent on re-audit (Brown et al, 1995).

Although historical data may not be totally accurate, they do highlight the trends in TB prevalence. There has been a marked decline since the beginning of this century in the incidence rates for TB. Notifications for TB in England and Wales declined from 117,139 in 1913 to 5,608 in 1995 (see Figure 4). The total UK figure for 1995 was 6,176. The incidence rate among males has consistently exceeded that for females, with male notification rates accounting for between 55 and 70 per cent of the total.

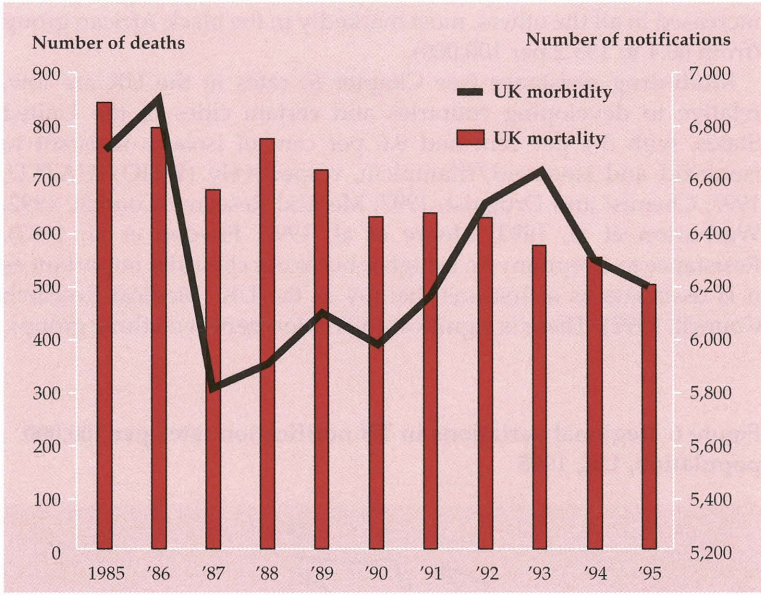
This century has generally been a period of significant and sustained decline in TB incidence levels. The apparent inconsistency between 1940 and 1950, when notifications increased, can be explained by the effects of World War II. The recruitment of large numbers of the civil population for national service, combined with the advent of mass miniature radiography, resulted in many cases of TB being identified that would not otherwise have been detected until a much later stage. The general downward trend has not continued, however, during the last ten years, which have seen a levelling out of TB notifications, albeit at a relatively low level. Indeed, small increases in notifications have been reported in some recent years (see Figure 5).

In contrast with the global picture, the increasing incidence of HIV does not appear to have had a large impact on UK TB levels. TB notification rates in England and Wales are highest among elderly white males and people from the Indian sub-continent, whereas the majority of AIDS cases are highest among white males in the 25-44 year old age group, who have a low risk of TB infection. The most recent national survey of TB in England and Wales estimated HIV prevalence among notified TB sufferers to be 2.3 per cent (Kumar et al, 1996). HIV prevalence was higher in London (4.3 per cent) than elsewhere (0.8 per cent). The true prevalence of co-infection may be higher (four to five per cent) than that reported in this survey due to selective undernotification[11] of TB in HIV infected patients.

There are wide variations in notification rates in the UK between regions (see Figure 6). At 26.2 per 100,000 the rate for North Thames

11 The anonymised unlinked testing showed 2.3% of those tested were HIV-positive, but some TB cases known to be HIV-positive were not included for testing and some persons with bacteriologically proven TB were not notified but were on the AIDS register.

Figure 5 **TB morbidity and mortality in the UK, 1985-1995**



Source: Office for National Statistics.

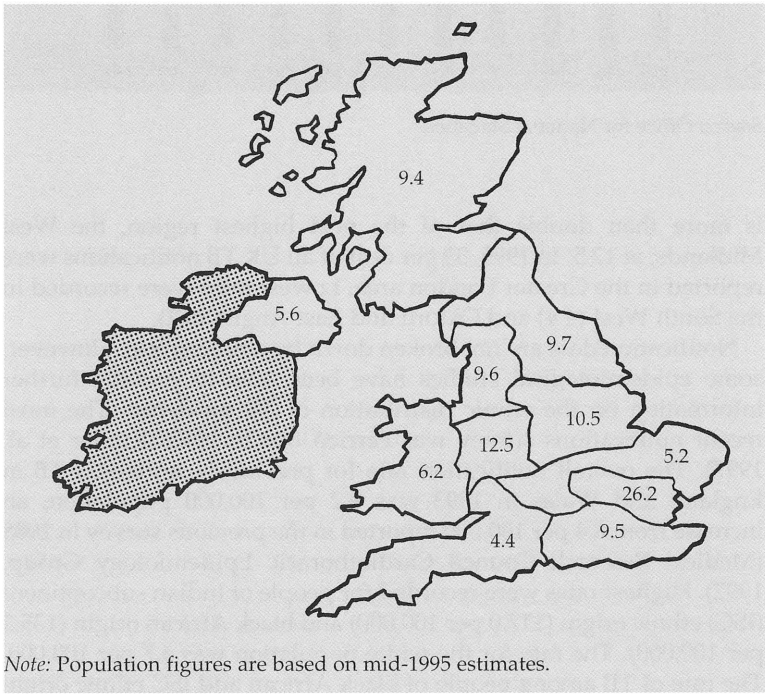
is more than double that of the next highest region, the West Midlands, at 12.5. In 1995, 33 per cent of all UK TB notifications were reported in the Greater London area. Lowest rates were recorded in the South West (4.4) and Oxford and East Anglia (5.2).

Notification data are not broken down by ethnic group. However, some epidemiological studies have been able to provide further information on the ethnic distribution of TB incidence. The most recent notifications survey was carried out in 1993 (Kumar et al, 1997). The overall notification rate for previously untreated TB in England and Wales in 1993 was 9.2 per 100,000 population, an increase from 8.4 per 100,000 reported in the previous survey in 1988 (Medical Research Council Cardiothoracic Epidemiology Group, 1992). Highest rates were recorded for people of Indian subcontinent (ISC) ethnic origin (117.0 per 100,000) and black African origin (135.2 per 100,000). The rate for the white population was 4.7 per 100,000. The rate of TB among people of black African and ISC ethnic origin varied depending on how long they had been resident in the UK. Highest rates were recorded among the most recently arrived

immigrants. In comparison with the 1988 survey, notification rates fell in the white, Indian and black Caribbean ethnic groups and increased in all the others, most markedly in the black African group (from 60.4 to 135.2 per 100,000).

Multi-drug resistance (see Chapter 6) rates in the UK are low, relative to developing countries and certain cities of the United States, with 3-4 per cent and 0.6 per cent of isolates resistant to isoniazid and isoniazid/rifampicin, respectively (WHO/IUATLD, 1997; Chemist and Druggist, 1997; Medical Research Council, 1992; Warburton et al, 1993; Moore et al, 1997; Frieden et al, 1993). Resistance to streptomycin is higher but is not clinically important as it is used less as a first-line therapy in the UK (Medical Research Council, 1992). There is significant variation between ethnic groups,

Figure 6 **Regional variations in TB notification rates per 100,000 population, UK, 1995**



Note: Population figures are based on mid-1995 estimates.

Sources: Office for National Statistics (England and Wales), Information and Statistics Division (Scotland), Regional Information Branch (N.Ireland).

though. A recent national survey reported resistance rates of 13 per cent among Black-Africans, 4.5 per cent among the Indian sub-continent ethnic group, 2 per cent among Whites and none among Black-Caribbeans in England and Wales (Ormerod et al, 1997). There is also geographical variation, with rates of resistance of 2.8 and 1.4 per cent being recorded in the North and South Thames regions, respectively (Warburton et al, 1993).

Mortality

TB mortality data are more accurate than corresponding morbidity data as the problems associated with disease notification are not relevant. There can, however, be problems in distinguishing deaths from TB from deaths with TB (death being due to a co-morbidity). In an audit of the treatment of 925 pulmonary cases notified in the 1993 Notification survey of England and Wales at outcome assessment 12 months after notification, 6.7 per cent had died, but only 1.5 per cent were deaths from TB; 5.2 per cent were deaths from co-morbidity (Ormerod et al, 1997).

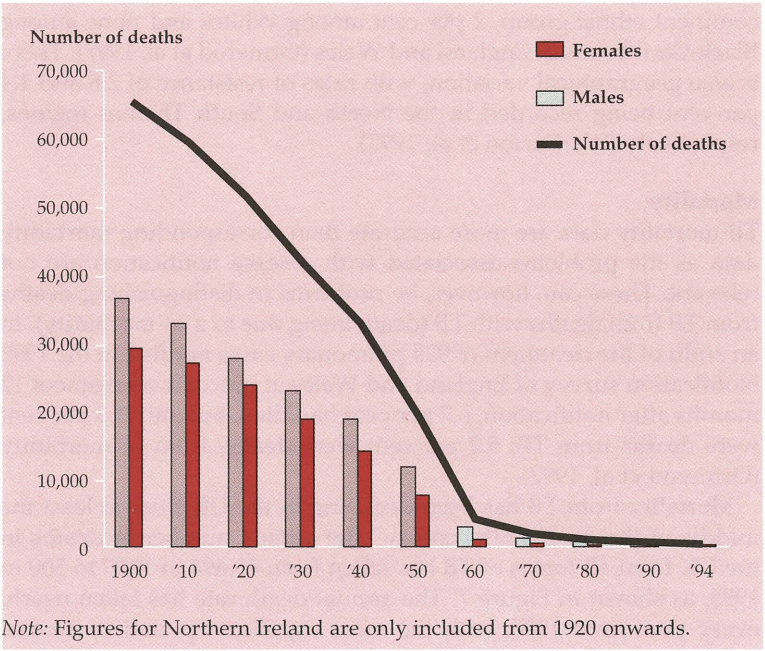
Mortality from TB has been declining in the UK from at least the middle of the nineteenth century. The annual number of deaths in the UK from all forms of TB has fallen from 65,694 in 1900 to 500 in 1995, as shown in Figure 7. The annual death rate has fallen nearly every year since 1900, with the most significant period of decline occurring up to around 1960. The inconsistencies reported in morbidity data during the 1940s are not reproduced with respect to mortality data. The rate of decline has slowed during the 1990s but, unlike notification levels, there has not been any reported increase in mortality levels.

The ratio of male to female TB deaths has mirrored the relationship of male to female notification rates, in that male deaths have accounted for between 55 and 70 per cent of the total number of deaths. There has been a shift in the age-profile of those dying with the disease. In the early 1900s, TB was principally a disease of the young. In 1900, 79 per cent of TB deaths in England and Wales occurred in people under the age of 45. Now it is the more elderly who are most susceptible to the disease. In 1995, 91 per cent of the people who died from TB were aged 45 years or over.

3.3 Summary

Approximately one-third of the world's population is infected with *Mycobacterium tuberculosis*. In 1990 a further 7.5 million infections and 2.5 million deaths were occurring annually, figures predicted to

Figure 7 **TB deaths in the 20th century, UK**



Note: Figures for Northern Ireland are only included from 1920 onwards.

Sources: Office for National Statistics; Northern Ireland Statistics and Research Agency; Information and Statistics Division, NHS in Scotland.

rise to about 10.2 million and 3.5 million, respectively, by the turn of the century. The majority of cases (up to 90 per cent) occur in developing countries but it is not just a developing country issue. Increasing notification rates are also being reported in industrialised countries.

Incidence rates are highest, and increasing, in South-East Asia and Africa. Much of the reported increased incidence is due to the impact of HIV. This is particularly the case with respect to Africa where HIV-attributed TB cases are estimated to increase from 194,000 (20 per cent of total cases) in 1990 to 604,000 (29 per cent) in 2000.

The 13.6 per cent increase in notifications that occurred in the UK between 1988 and 1993 followed a period of near continual decline throughout the twentieth century. The increase that did occur was concentrated among certain ethnic groups and in particular geographic areas. The largest increase in notifications was in the Indian sub-continent (ISC) ethnic group. The largest relative increase

was among individuals of Black African ethnic origin. Rates in these groups were 20-30 times higher than those in the white population. Inner-city regions, particularly in London and the West Midlands, had vastly higher notification levels than rural areas.

In contrast with the world-wide situation, HIV has not, to date, had much of an impact on notification levels in the UK. Only 2.3 per cent of TB notifications are for HIV-infected persons. The growth of the UK population of Indian subcontinent ethnic origin and from other endemic TB areas has had a greater influence on rising notification rates. Epidemiological data indicate, however, that socio-economic factors are the major influence, with the rise in TB levels affecting only the poorest areas. TB continues to be strongly correlated with poverty.

4 DIAGNOSTIC PROCEDURES

Even in developed countries, it is still often the case that TB is either misdiagnosed or goes unrecognised. A correct diagnosis may not be made until after a patient's death. Part of the problem is that many of the diagnostic tests cannot unequivocally confirm the presence of TB. Additionally, many of the symptoms associated with clinical TB are also associated with other illnesses, such as bronchitis and cancer. The diagnostic tests currently available are described below.

4.1 Established techniques

Tuberculin skin-tests – These tests are an indicator of infection and not necessarily of disease. The tests involve the patient being directly exposed to the tubercle bacillus and measure the degree of tuberculin hypersensitivity in the patient. A positive skin test is associated with acquired immunity and is evidence of either a previous primary infection or immunisation with the BCG vaccine (see Chapter 5). The greater the strength of the tuberculin reaction the more likely an individual is to have active disease. The correlation between tuberculin status and outcome is valid for large population groups. However, for an individual the validity of the tests for both diagnosis and prognosis is much reduced.

Skin-tests are used most for estimating the prevalence of tuberculous infection and the annual rate of infection within a sample population. One survey will indicate the prevalence of infection. Repeated tests on tuberculin negative individuals will generate the annual rate of infection. There are three tests in common use: the Mantoux test, the Heaf test and the Tine test.

Mantoux test: This is performed by injecting intradermally 0.1 ml of a tuberculin dilution into the forearm. The injection produces a reaction of erythema (inflammation of skin) and induration (thickening of skin). The diameter of the induration is read 48-72 hours after injection. The area of erythema is irrelevant. The test is regarded as positive if the induration is 10 mm or greater. Infected patients with a reduced immune response mechanism may produce a negative test result as the patient is unable to develop a hypersensitivity response.

Heaf test: Injection of tuberculin is performed with a Heaf gun which punctures the skin to a depth of 2 mm with six spring-loaded needles. Results are established between three and seven days after injection and are graded as follows:

Grade 1 – Palpable induration around at least four papules

Grade 2 – Papules are larger and have formed a ring of induration
Grade 3 – Induration has spread to fill the centre of the ring
Grade 4 – Grade 3 with additional vesiculation (ulceration of the skin)

Grades 2-4 are regarded as positive in the absence of previous BCG. When BCG has been previously administered grades 3-4 are regarded as positive. The Heaf test is of use for mass screening, such as checking the contacts of an infectious patient.

Tine test: This is a multi-puncture test performed with a disposable unit which consists of 4 small tines coated with tuberculin. The test is read between 48 and 72 hours after injection and is graded similarly to the Heaf test. The test is relatively expensive, yet simple to use and less painful for children. Tuberculin hypersensitivity may be reduced by severe illness, old age, chronic disease and overwhelming TB.

Radiology tests – X-rays, in addition to tuberculin skin testing, are a commonly used diagnostic tool for TB in developed countries. X-rays of pulmonary TB vary in appearance between primary and secondary TB. Primary infection in the lung produces a pneumonia which appears as an area of consolidation on the X-ray. The consolidation is generally singular and can vary in its size and its location within the lung. Secondary TB is also a pneumonia and as such the general X-ray appearance is also one of consolidation. However, the X-ray appearance of secondary TB differs from that of primary TB in several ways. There are likely to be multiple areas of consolidation separated by normal lung, the distribution of the disease is greater and there are often areas of cavitation and calcification.

Once a lesion has been identified as probably tuberculous, a further test is required to gauge whether the lesion is still active. A second X-ray, three to four weeks after the first, will determine whether or not the lesion has grown. Even if the lesion has not grown between the period of the two X-rays, there is a strong likelihood that tubercle bacilli may still be present within the lesion, particularly if the patient has not previously received treatment.

Tomography[12] may be appropriate on occasions when an X-ray produces an unclear image, as it enables a clearer view of the lesion to be made than is possible with X-ray.

Sputum tests – Examination and culture of sputum forms the cornerstone of diagnosis of TB. Testing is generally undertaken using auranine rhodamine stain, a fluorescent dye technique. The Ziehl-Neelsen staining technique is used as a complementary check

12 Method of radiography displaying details in a selected plane within the body.

for positives. This has a specificity[13] of over 99 per cent and a sensitivity[14] of approximately 55 per cent in pulmonary TB (Yeager et al, 1967). Once mycobacterium has been identified, the sputum cultures should be tested for sensitivity to anti-TB medicines (drug-resistance) so that appropriate treatment can then be administered.

4.2 New techniques

The delay in determining diagnosis from culture, which may have a detrimental impact on patient outcome, has encouraged research into the use of molecular diagnostic techniques. Numerous techniques have been tested since the mid 1980s. Those offering most grounds for optimism are outlined below.

Polymerase chain reaction (PCR) – PCR involves the identification of a sequence of DNA within the gene of the mycobacterium and amplifying it by a factor of about 10^9. Electrophoresis[15] is then used to identify the amplified product. At present it is widely regarded that the technique does not have the specificity and sensitivity rates of conventional laboratory methods (Ellner et al, 1993), although some studies have reported results to the contrary (Wilson et al, 1993; Pierre et al, 1991). PCR is also susceptible to contamination which can create false-positives. A 1994 study (Noordhoek et al, 1994) compared the abilities of seven laboratories to detect mycobacteria in 200 sputa. Sensitivity and specificity varied widely between laboratories with false-positive rates ranging from 0-70 per cent.

Restriction fragment length polymorphism (RFLP) – The discovery of a DNA pattern that is repeated throughout the genome[16] of *Mycobacterium tuberculosis* enabled the development of DNA 'fingerprinting' for identifying individual isolates (Zainuddin et al, 1989). RFLP is of particular use for investigating outbreaks of TB as strains which produce indistinguishable fingerprints imply a single source of infection. RFLP has been used in a number of recent studies to investigate the spread of drug-resistant disease and new infection among HIV-positive patients (Tabet et al, 1994; Dooley et al, 1992; Edlin et al, 1992). The usefulness of RFLP as a diagnostic and epidemiological tool is restricted among Africans as they have a greater level of homogeneity in their isolates than Europeans and North Americans (Drobniewski et al, 1994).

13 The extent to which a method gives results that are free from false positives.
14 The extent to which a method gives results that are free from false negatives.
15 Movement of dispersed particles in a fluid under the influence of an electric field.
16 Total gene complement of a set of chromosomes.

4.3 Potential for screening programmes

Mass screening of the general population by X-ray has long been regarded as an ineffectual method for controlling TB (Krivinka et al, 1974). It has been estimated that 10,000 radiographs lead to the detection of only one case of TB (Swallow et al, 1972). The poor detection rate and high cost associated with X-ray led to the abandonment of mass radiographic screening for pulmonary TB in the UK in the 1960s. Skin-testing is now the favoured method for case-finding in large populations, even though skin-testing is only an indicator of infection not disease.

The inappropriateness of radiography as a mass screening tool has not diluted a widely-held view that screening of selected subpopulations is a valid case-finding method (American Thoracic Society, 1983; WHO Expert Committee on Tuberculosis, 1974). The British Thoracic Society recommends, for instance, that new immigrants should be screened for TB as they are associated with raised levels of TB (Joint Tuberculosis Committee, 1978; Medical Research Council Tuberculosis and Chest Diseases Unit, 1985). Screening of new immigrants to the UK identifies approximately 1:150 with clinical disease but up to 35 per cent who will be tuberculin negative and can be vaccinated (Ormerod, 1990).

A study of 970 alcoholics and drug addicts in New York City demonstrated a rate of active TB among this subpopulation to be 28 times greater than for the age-matched general population of the city (Friedman et al, 1987). Screening only those people with a cough and a positive skin-test increased the rate of detected active TB to 225 times the New York City rate. Other selected populations in which raised levels of TB have been recorded, thus making them potential screening targets, include contacts of the source case (Capewell et al, 1984; British Thoracic Association, 1978); and the elderly in nursing homes (Stead et al, 1985).

4.4 Summary

Microscopy of stained smears and culture of sputum remain the cornerstones of diagnosis of TB. However, the ability of molecular techniques to produce diagnostic results and evidence on drug resistance relatively quickly means that they are likely to supersede conventional laboratory methods in the future, particularly in developed countries. Earlier diagnostic results permit more effective therapy and better patient outcome. The relatively high cost of the molecular techniques, and the greater degree of sensitivity and specificity currently attainable by conventional methods means that this transition is unlikely to be immediate.

5 CONTROL AND PREVENTION OF TB IN THE UK

5.1 UK guidelines

To be effective, prevention programmes require the prompt diagnosis and successful treatment of infectious individuals, so that the chain of disease spread can be broken. Guidelines for the control and prevention of TB in the UK are issued by the Joint Tuberculosis Committee of the British Thoracic Society. This Code of Practice was revised in 1994, to take account of new evidence concerning contact tracing, drug-resistant disease and the relationship between HIV infection and TB (Joint Tuberculosis Committee of the British Thoracic Society, 1994). The revised guidelines are:

1. All cases of TB must be notified. This is a) to provide data to monitor epidemiological trends and b) to trigger contact tracing.
2. Certain patients need hospital admission. A few patients with smear positive pulmonary disease will require hospital admission for severe illness, adverse effects of chemotherapy, or social reasons.
3. Patients with positive sputum smears and sensitive organisms should be considered infectious until they have received two weeks' chemotherapy.
4. Treatment of all TB patients should be supervised by a respiratory physician employing standard medication guidelines and monitoring compliance at least monthly.
5. Health care workers at risk should be protected by BCG vaccination and appropriate infection control measures, and evidence of infectious TB should be sought among prospective NHS staff, school teachers and 'others'. Staff protection includes pre-employment screening, recording of tuberculous symptoms, details of previous BCG vaccination and tuberculin skin testing and chest radiography where indicated.
6. Protection of prison staff. TB is rare in HM prisons, with no episode of transmission of TB within a UK prison being recorded (Darbyshire, 1989; HM Prison Service, 1993). To maintain this record, new staff should be treated in the same manner as health care workers at risk. Smear positive prisoners should be segregated as for smear positive hospital inpatients.
7. TB should be considered in the elderly in long stay care with persistent chest symptoms. New admissions to nursing homes should all be considered candidates for reactivation TB. Evidence of previous infection should be noted and residents displaying symptoms suggestive of TB should be investigated.

Study evidence indicates that the risk of TB infection is lower in UK than in US nursing homes (Nisar et al, 1993; Welty et al, 1985).

8. Contact tracing should be vigorously pursued with chemoprophylaxis, BCG vaccination, or follow-up where applicable. Studies estimate that approximately 10 per cent of TB cases are diagnosed by contact tracing and that disease occurs in about 1 per cent of all contacts (Hussain et al, 1992).
9. Entrants to the UK from high risk countries (TB incidence >40/100,000 population per year) should be screened. The incidence of TB in indigenous white residents of England per 100,000 population was 4.7, compared with 135 in Indians, 101 in Pakistani/Bangladeshis, and 29 in Afro-Caribbeans (Medical Research Council, 1992). Screening would detect infected patients requiring chemoprophylaxis and uninfected persons who may require BCG vaccination (Ormerod, 1990).
10. BCG vaccination should be offered where appropriate but not in subjects with known or suspected HIV infection.
11. The local organisation of TB services should be strengthened and should include adequate nursing and support staff.
12. Contracts between purchasers and providers should specify management of TB in line with this and other Joint Tuberculosis Committee guidelines.

These guidelines were modified in 1997 to try and prevent undernotification (Ormerod et al, 1997b).

5.2 Prevention – the role of BCG vaccination

BCG vaccination is a key component of the UK guidelines outlined above. It has become the most widely used TB preventative measure since its introduction as a vaccination in 1921. There are various strains of BCG vaccine in use today but they all contain a mild strain of the bacillus *Mycobacterium bovis* and originate from the initial strain developed by Calmette and Guerin at the beginning of this century. BCG vaccination produces the immunity in an individual that is normally acquired by primary infection, without the subsequent risk of disease (see section 2.3). As such, BCG is only of benefit to people who are uninfected. It offers no protection to those people who have been infected and have, therefore, already built up immunity or developed active disease. A tuberculin skin test should therefore be carried out before the vaccine is administered[17]. Those

17 The exception to this rule is infants up to three months old who may be immunised without a prior test as long as they have had no previous contact with TB.

with a positive test should not be given BCG as it is unnecessary and may cause a larger reaction. BCG does not give lifelong protection as there is a gradual decline over time in the degree of immunity following vaccination. However, for the same reasons that BCG is only of benefit to people who are not infected, there would be no benefit to an individual receiving a second BCG vaccination once the protection afforded by the initial vaccination has worn off.

The vaccine is administered intradermally (subcutaneous injection may result in abscess formation). A small localised lesion will appear but will heal within 6-12 weeks. A reduction in immunity occurs immediately after vaccination and so exposure to TB should be avoided at this time. Relative immunity is acquired after a short period of time. Tuberculin tests after BCG usually but not invariably become positive. Research by Hart et al (1967) has shown that the protective factor is the presence of the BCG scar not the tuberculin response. As such, those with a scar and a negative tuberculin test have the same degree of protection as those with a scar and a positive tuberculin skin test. The side-effects of vaccination are rare if attention is paid to correct selection of subjects and to the vaccination techniques but include inflammation of the lymph glands, TB of the skin, inflammation of the bone, and 'BCG-itis'. Contraindications to vaccination are severe immuno-deficiency (including known HIV-positivity) and pregnancy.

BCG coverage

Promotion from the WHO meant BCG vaccination came into world-wide use during the 1950s, despite uncertainty over its clinical effectiveness, and it is now the most widely used vaccine in the world. In 1993 BCG immunisation was carried out in 172 countries, with up to 92 per cent of infants in these countries receiving the vaccine (WHO, 1995). There is, however, wide variation between countries in both the extent of use of BCG and the manner in which it is used. This reflects the continuing uncertainty over the effectiveness of the vaccine in preventing TB. The USA and the Netherlands, for example, have always opposed a community-wide vaccination programme and other countries, such as Sweden, have abandoned or modified their own programmes.

The UK government, however, remains committed to an extensive vaccination programme. The vaccine has been in general use in the UK since 1953, when the target was to immunise all children at age 13. Thirty-five per cent of the target group were being immunised each year by 1958, 60 per cent by 1962 (Department of Health, 1996a). Approximately 75 per cent of the target group are now being

immunised annually. In addition, neonatal immunisation programmes cover up to 50,000 neonates per year. The groups currently recommended for immunisation with BCG in the UK are shown in Box 1.

Box 1 **Groups recommended by the Department of Health for immunisation with BCG**

1 Those at higher risk of TB

1.1 Health service staff who have contact with infectious patients or their specimens.
1.2 Veterinary and other staff who handle animal specimens known to be susceptible to TB.
1.3 Staff of prisons, old people's homes, refugee hostels and hostels for the homeless.
1.4 Contacts of cases known to be suffering from active pulmonary TB.
1.5 Immigrants from countries with a high prevalence of TB, their children and infants wherever born.
1.6 Those intending to stay in Asia, Africa, Central or South America for more than a month.

2 Those at 'normal' risk of developing TB

2.1 School children between the ages of 10 and 14 years.
2.2 Newly-born babies, children or adults where the parents or the individuals themselves request BCG immunisation.

Sources: Department of Health, Welsh Office, Scottish Office, Department of Health and Social Services (Northern Ireland), 1996.

The community-wide teenage vaccination programme in operation in the UK contrasts sharply with programmes in other countries (see Box 2). In most countries vaccination is based upon the recommendations of national health authorities, although some countries operate a system of compulsory immunisations governed by legislation, such as France and the countries of Central and Eastern Europe. The most common method of BCG vaccination is a single dose at birth, as recommended by the WHO Expanded Programme on Immunisation. This method is used mainly in developing countries where the incidence levels are relatively high. Such a policy is particularly effective against the serious, disseminated forms of TB such as tuberculous meningitis and miliary disease. Some countries have adopted a system of revaccination and in certain regions, particularly in Eastern Europe,

Box 2 **TB immunisation schedules of selected countries**

Country	Schedule
Albania	At birth; 6 years
Austria	Groups at risk
Belgium	No schedule
France	<6 years; <18 years
Germany	At birth
Ireland	At birth; 12 years
Norway	13 years
Portugal	At birth; 5 years; 11 years
Russian Federation	4-7 days; 7 years; 14-15 years; 27-30 years
Spain	No schedule
UK	At birth; 11-14 years

Source: WHO Weekly Epidemiological Record, 1995.

employ a system of multiple revaccinations throughout childhood. There is no evidence, however, that BCG revaccination works (see page 36). Finland has shown no increase in childhood TB since revaccination at age six was dropped (Tala-Heikkila, 1993). Very few countries recommend a programme similar to that in the UK where vaccination is normally first carried out between the ages of 11-14.

Efficacy of BCG vaccination

The variation in immunisation programmes between countries highlighted in Box 2 reflects the disparate results of studies which have evaluated the efficacy of BCG vaccination. Twenty-one controlled clinical trials of the efficacy of BCG vaccines were carried out in 10 countries between 1927 and 1968 (WHO, 1995). The protective efficacy[18] ranged from zero (perhaps even negative) to 80 per cent in the 19 completed trials. However, only eight of these trials were carried out in an acceptably controlled fashion (Springett, 1965; Hart, 1967; Eickhoff, 1977). The results of these eight randomised controlled trials (RCTs) from around the world are presented in Table 6 and Figure 8.

Protective efficacy in these studies ranged from 80 per cent to –56 per cent. The most recent and largest trial was carried out in Chingleput, India, in 1968. BCG vaccines and placebo were

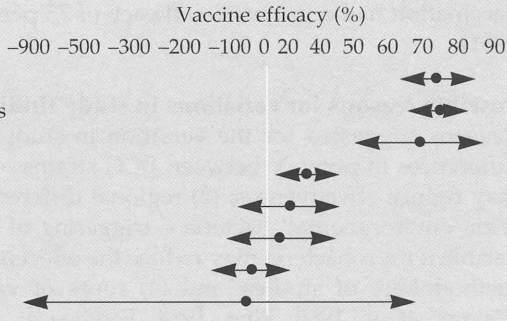
18 This is the term generally used for establishing the effectiveness of vaccines and is defined as the percentage reduction in risk of disease among vaccine recipients when compared with similarly exposed non-vaccinated people.

Table 6 **Results of major BCG immunisation trials**

Trial	*Year*	*Age group*	*Follow-up, years*	*Subjects in trial*	*Protective efficacy %*
North American Indians (Stein & Aronson, 1953)	1935-38	0-20 years	9-11	3,008	80
Chicago (Rosenthal et al, 1961)	1937-48	Under 3 months	12-23	3,381	75
Georgia-USA (Comstock & Webster, 1969)	1947	6-17 years	20	4,839	–56
Puerto Rico (Palmer et al, 1958)	1949-51	1-18 years	5.5-7.5	77,972	31
Georgia-Alabama (Comstock & Palmer, 1966)	1950	5 years and over	14	34,767	14
Great Britain (Medical Research Council, 1972)	1950-52	14-15.5 years	20	32,282	76
Madanapalle (Frimodt-Moller et al, 1968)	1950-55	All ages	9-14	10,877	31
Chingleput (WHO, 1979)	1968	All ages	7.5	115,000	–32

Source: Adapted from Clemens et al, 1983.

Figure 8 **Estimates from eight RCTs of the efficacy of BCG vaccines against TB**



Note:
Efficacy is expressed on a logarithmic scale with arrows indicating 95% confidence intervals.

Source: Adapted from Fine et al, 1990.

randomly allocated to approximately 260,000 individuals, of whom 115,000 were definitely tuberculin negative at the time of vaccination (Tuberculosis Prevention Trial, 1979). The results of the trial indicated that BCG offered no protection during the follow-up period after vaccination. A similar finding of little or no protection from BCG vaccination was recorded in two trials in the southern United States and is a major contributory factor to the USA not introducing a community-wide vaccination programme (Comstock et al, 1969; Comstock et al, 1976). The larger of these trials began in 1950 and involved 64,136 people, of whom 34,767 were eligible for investigation. The 'usefulness' of BCG in the trial was established based on three criteria:

1. the percentage of TB cases in the population arising from tuberculin negative people;
2. the effectiveness of vaccination among the eligible portion of this population;
3. the reduction in TB that could be expected to result from vaccination of all eligible people.

The study estimated that only 26.4 per cent of TB cases could have been prevented if there had been a wholly effective vaccine. After 14 years of follow-up there was only a 14.2 per cent reduction in TB cases among vaccinees compared with controls. Vaccination of all tuberculin negative people would have prevented only five per cent of the expected number of cases if vaccination was not given. BCG was also least effective among the subgroups with the highest case rates (blacks). The findings of the two studies from southern USA contrasted with an earlier American study, based on 3,381 infants born in a Chicago hospital between 1937 and 1948, in which BCG vaccination had a protective efficacy of 75 per cent (Rosenthal et al, 1961).

Possible reasons for variations in study findings

Reasons suggested for the variation in study findings include: (1) differences in potency between BCG strains – weak vaccine strains may reduce effectiveness; (2) regional differences in prior infection with 'environmental' bacteria – triggering of immune response by harmless mycobacteria may reduce the effect of BCG; (3) flaws in the methodology of studies; and (4) route of vaccine administration (Palmer et al, 1966; Fine, 1988; Ferebee et al, 1966; Hart, 1967). Although reasons for the variations in estimated efficacy of BCG have been postulated, there still remains no consensus on the issue and, thus, countries continue to carry out very different programmes.

UK study findings

The strongest evidence supporting the use of BCG vaccination has probably come from trials and surveys carried out in Great Britain. The Medical Research Council's controlled trial of TB vaccines, which began in 1950, is the largest RCT to report a high protective efficacy of BCG (Medical Research Council: 1956; 1959; 1963; 1972; Hart et al,1977). 26,465 out of 54,239 14-15 year old participants who entered the trial in 1950-2 were tuberculin negative and randomly allocated to a BCG vaccinated or unvaccinated group and followed-up for 20 years. The number of TB cases developing during the study period was significantly higher in the unvaccinated group (248) than in the vaccinated group (62) (see Table 7). The annual incidence of TB decreased substantially during the trial period with 60 per cent of all cases occurring in the first five years. Thus, incidence was higher among 15-20 year olds than 30-35 year olds. The decline was particularly apparent in the unvaccinated group. Although there was an initial rise, the number of cases approximately halved every two and a half years.

Over the whole period the average annual incidence was 0.98 per 1,000 in the unvaccinated group and 0.23 per 1,000 in the vaccinated group (see Table 8). The decreasing number of annual cases reported was reflected in a decline in the annual incidence per 1,000 participants for each successive five-year period. The large difference that existed between the unvaccinated group and the vaccinated group for the first five years (2.50 vs. 0.40) had evaporated by the last five year period (0.08 vs. 0.09). As such the

Table 7 **Incidence of TB in trial participants according to interval between entry and starting point of disease**

Trial group	*No. of participants*	*No. of cases of TB per 2.5 year period*								
		Total	0-2.5	2.5-5	5-7.5	7.5-10	10-12.5	12.5-15	15-17.5	17.5-20
Negative, unvaccinated	12867	248	68	92	41	26	11	5	2	3
Negative, BCG vaccinated	13598	62	14	13	13	9	2	5	3	3

Note: Starting point of disease is determined by radiographic or clinical manifestation.

Source: Hart et al, 1977.

Table 8 **Annual incidence of TB per 1,000 participants and protective efficacy of vaccination**

Trial group	*Annual incidence of TB per 1,000 participants* and protective efficacy of vaccination according to interval since vaccination*				
	0-20	0-5	5-10	10-15	15-20
Negative, unvaccinated	0.98	2.50	1.06	0.26	0.08
Negative, BCG vaccinated	0.23	0.40	0.33	0.10	0.09
BCG protective efficacy (%)	77	84	69	59	–12

Note:
*After allowing for removals from population at risk due to death or contracting TB.

Source: Hart et al, 1977.

protective efficacy of vaccination also showed a decline over time, although it equated to 77 per cent over the whole trial period (results for the last five year period do not possess the statistical significance that the other periods possess as they are based on a small number of cases). The protection offered by BCG vaccine extended to all forms of TB and was total for tuberculous meningitis and miliary pulmonary TB. Protection was similar for both sexes.

The results of this trial clearly demonstrated the benefit of BCG vaccination for 15 year olds in 1950-2 in reducing TB incidence levels. It also demonstrated that BCG is likely to provide little or no benefit 15-20 years after vaccination. The convergence in incidence rates in the two groups may have resulted from:

- an increase in the level of resistance in the unvaccinated group as a result of natural infections by tubercle bacilli and other mycobacteria, or the withdrawal of those particularly susceptible because they contracted TB;
- a gradual decrease in the level of resistance in the vaccinated group as a result of a decline in the efficacy of the vaccine;
- both effects combined.

The efficacy of BCG vaccination in the UK has also been demonstrated in a series of surveillance studies on the national immunisation programme for children aged 10-13 (British Thoracic and Tuberculosis Association, 1975; British Thoracic Association, 1980; Sutherland et al, 1987). These were not RCTs but were comparisons of TB incidence rates between people given BCG as part of the national scheme and those who did not receive BCG. Estimated protective efficacy was similar in all three studies, ranging

Table 9 **Estimated protective efficacy of BCG vaccination in four cohorts at ages 15-19 and 20-24 years in England & Wales**

Population cohort	*Period during which the cohort was aged 13 years*	*Population eligible for the schools' BCG scheme, aged 15-19 (000s)*	*Total TB cases in survey year*		*Protective efficacy (%)*	
			Ages		*Ages*	
			15-19	*20-24*	*15-19*	*20-24*
MRC vaccines trial	1949-51	54	361	158	84	69
England and Wales	1967-71	3,127	259	206	87	77
England and Wales	1972-76	3,656	228	244	67	70
England and Wales	1977-81	3,916	163	+	80	+

Note:
+ Cohort not yet old enough

Source: Sutherland et al, 1987.

from 67-87 per cent (see Table 9). These figures closely mirrored the efficacy recorded in the Medical Research Council's RCT, thus indicating that protective efficacy has not diminished significantly since the start of the schools' scheme.

The UK government has recently reaffirmed its commitment to the schools programme for BCG vaccination (Department of Health, 1996a). This policy commitment comes at a time when the value of the programme has been questioned. Although vaccine efficacy has remained relatively constant – and high – since the 1950s, the prevalence and incidence of TB in the UK are now significantly lower than was the case in 1953 when the school vaccination programme started (see section 3.2), resulting in a corresponding reduction in the benefit that can now be expected from the national scheme compared with 1953. TB prevalence in the groups likely to be given BCG at age 13/14, i.e. white ethnic, is now very low; approximately 2/100,000 per annum. Higher prevalence ethnic groups should have been vaccinated either at birth or as new immigrants (see Box 1, section 5.2). The debate over what format, if any, the schools programme should take is discussed in detail in section 7.4. Specifically, the current cost-effectiveness of the programme is assessed.

6 TREATMENT

6.1 History of treatment

Early forms of treatment

Specific treatment for combating TB only became available with the development of chemotherapy in the 1950s. Earlier treatment centred on methods to improve the resistance level of patients, such as promoting rest and 'appropriate' nutrition. By the end of the 19th century these techniques had developed into the formalised sanatorium regime, which was the mainstay of treatment for the first half of the 20th century. This approach was augmented by the use of collapse therapy. Such therapy attempted to collapse the affected part of the lung, so allowing closure of cavities, a reduction in bacterial numbers and healing. Although collapse therapy was in common usage, with various techniques being employed, its clinical justification was unproven.

Early treatment was deemed successful if a patient's sputum was free from tubercle bacilli and the disease no longer regarded as progressive. A patient, however, would continue to harbour bacilli in apparently healed lesions and there was a constant threat of recurrence. Reductions in the incidence and mortality of TB during the first half of the 20th century owed far more to improvements in the general health and living standards of the population than to the treatment methods used.

Advent of anti-TB medicine therapy

The objectives and outcomes of TB treatment were revolutionised with the introduction of anti-TB medicines in the 1950s. Treatment was now capable of producing a permanent cure of the infection. The first stage of change came with the discovery of streptomycin by Waksman in 1941. In 1944 Waksman recognised the ability of streptomycin to act against *Mycobacterium tuberculosis*, with the first clinical trials being reported in 1945. The initial trials provided favourable results, although relapse was often apparent and acquired resistance was occurring.

The importance of using more than one medicine (chemotherapy) was tested in a 1948 Medical Research Council study comparing streptomycin plus para-amino salicylic acid (PAS), a second anti-TB medicine to be identified, with streptomycin alone. The dual therapy was associated with a much lower level of resistance and underlined the key role of chemotherapy in combating TB. Isoniazid was first used in clinical trials in 1952 and due to its potency, non-toxicity and

cheapness quickly became the most widely used medicine.

Effective chemotherapy was generally available by the beginning of the 1960s. 'Classical chemotherapy' consisted of 18-24 months of treatment with streptomycin, isoniazid and PAS. This was a very effective regimen, although there was a high incidence of side-effects. The relatively long duration of a course of this regimen did not encourage patient compliance, however, so increasing the likelihood of drug-resistant TB occurring. As such, there was increased emphasis on developing a 'short-course' chemotherapy regimen (Fox, 1985; Stead et al, 1985). Options for short-course regimens increased with the development of other anti-TB medicines, most notably rifampicin and ethambutol, which replaced PAS. Indeed, the introduction of rifampicin enabled the first effective nine-month short-course regimen to be developed (British Thoracic and Tuberculosis Association, 1976).

Anti-TB medicines can be categorised as either first-line medicines or reserve medicines. First-line medicines are used in initial and maintenance chemotherapy. Reserve medicines are used for the treatment of patients with known or suspected drug resistance. The reserve medicines tend to be less clinically effective and/or are associated with more severe adverse effects. The adverse effects associated with antituberculous medicines are shown in Box 3. The more first line medicines that are used in a regimen, the more likely that regimen is to be effective and the shorter will be the duration of chemotherapy, possibly as short as six months.

Rationale of chemotherapy

Different populations of bacteria exist within tuberculous lesions. These bacteria have varying characteristics, such as their speed at multiplying, and are likely to be more susceptible to certain anti-TB medicines than others (Fox, 1980). For instance, isoniazid is particularly effective against rapidly growing bacilli. Rifampicin is able to kill both actively multiplying and relatively dormant bacilli (Dickinson et al, 1981). Pyrazinamide is most effective in an acid environment. It is believed, though, that there are some totally dormant bacilli which cannot be killed by any medicine.

The first two weeks of chemotherapy treatment produce a 90 per cent fall in the number of bacilli detected in the sputum of patients treated with isoniazid, rifampicin, streptomycin and pyrazinamide. Sustained chemotherapy, however, is required to kill the remaining 10 per cent of the relatively dormant bacilli. Failure to kill all of these multiplying bacilli can lead to recurrence and drug-resistance.

The British and American Thoracic Societies both now recommend

Box 3 **Adverse effects of anti-TB medicines**

Medicine	Potential adverse effects
First-line medicines	
Isoniazid	Peripheral neuropathy, hepatitis, psychosis
Rifampicin	Transient disturbance of liver function, liver toxicity, reduced effectiveness of oral contraceptives and other drugs
Ethambutol	Visual disturbances
Pyrazinamide	Liver toxicity, skin reactions
Streptomycin	Ototoxicity
Reserve medicines	
Thiacetazone	Gastro-intestinal, skin reactions
PAS	Gastro-intestinal, febrile and skin reactions
Ethionamide/Prothionamide	Gastro-intestinal, metallic taste in mouth
Cycloserine	Mainly neurological, including headache, drowsiness, convulsions
Cipro- or O-floxacin	Abdominal discomfort, headache, tremulousness
Azithro- or Clarithro-mycin	Gastrointestinal upset
Capreomycin	Ototoxicity
Clofazimine	Headache, red skin discolouration

Source: Adapted from British National Formulary, 1997 and Seaton et al, 1989.

the following six-month adult regimen (Subcommittee of the Joint Tuberculosis Committee, 1990; American Thoracic Society, 1994):

1. Isoniazid 300 mg daily by mouth, combined with:
2. Rifampicin 600 mg daily by mouth (or 450 mg daily if the body weight is less than 50 kg). Isoniazid and rifampicin are given together in a combined tablet in appropriate dosage, to prevent one medicine being taken without the other. Both these medicines are given every day for the full six months.

In addition, the first two months of this regimen include:

3. Pyrazinamide 1.5 g daily by mouth in those weighing under 50 kg, or 2.0 g daily by mouth if 50 kg or over, combined with:
4. Ethambutol 15 mg/kg daily by mouth.

6.2 Control programmes

The development of effective chemotherapy regimens means that, in principle, permanent cure can be realised in all cases. Failure to achieve this is likely to be the result of poorly designed or

implemented programmes, which may be the fault of either the doctor or the patient. Poor compliance continues to be the main cause of relapse both in the developed and developing world (Ormerod et al, 1991; Grzybowski et al, 1978). Patients frequently lose their incentive to continue taking medication once the coughing and other symptoms have gone, which happens before the full six-month duration of treatment has been completed.

Inadequate or incomplete treatment causes greater problems than administering no treatment at all, as multidrug-resistant TB (MDR-TB) develops, some strains of which are resistant to all the current anti-TB medicines. MDR-TB is defined as resistance to isoniazid and rifampicin with or without other anti-TB drugs. Strains of MDR-TB are treated initially with at least three medicines to which isolates are sensitive until a negative sputum smear is obtained. Treatment with two of these medicines continues for a further nine months and may involve the use of 'reserve' medicines (see Box 3). Such a regimen increases treatment costs. The cost of care for multidrug-resistant patients has been estimated to be as high as $US180,000 (1993 prices) in the US, compared to around $2,000 for a person without resistance (Mahmoudi et al, 1993).

The development of new TB medicines will help to combat resistance, but it is an area that has been largely neglected by researchers. Medicines for diseases impacting predominantly on inhabitants of first world countries generally offer pharmaceutical companies higher rates of return on research and development expenditure. However, Hoechst Marion Roussel is currently conducting trials of rifapentine in Canada, South Africa and the USA, which, assuming favourable trial results, will be the first new medicine for treating TB in almost 30 years. Glaxo Wellcome is sponsoring a research initiative, 'Action TB', which has several programmes of research ongoing in academic centres world-wide. The search for both new drugs and an effective vaccine is likely to be aided by recent advances in mycobacterial molecular genetics – the whole TB genome was sequenced in November 1997 – which allow scientists to isolate and manipulate TB genes.

The problems associated with poor compliance have encouraged the development of the WHO's strategy for curing TB patients: directly-observed treatment, short-course (DOTS). DOTS is a system where health care workers ensure each patient takes the correct medication for the required six-month period. The treatment regimen is the same as that recommended by the British and American Thoracic Societies. No hospitalisation is required and patients can continue to work throughout the period of treatment.

This strategy is designed for all TB-infected people but is perhaps most appropriate in developing countries where patients may be quicker in curtailing treatment once the symptomatic phase is over.

The primary aim of the WHO's TB programme is to advise countries on how to implement DOTS control programmes correctly. It currently has the capacity to advise approximately 10 countries per annum. The DOTS strategy has five basic features (TB Treatment Observer, 1996):

- political commitment;
- sputum microscopy to diagnose cases;
- direct observation of treatment to ensure patients actually take their medicines;
- reliable, high-quality supply of drugs; and
- rigorous monitoring and evaluation of treatment.

DOTS programmes have been implemented in Africa, Asia, North and Latin America. China, which accounts for almost a quarter of the world's TB cases, is one country which has already benefited from a DOTS programme. In April 1991, a TB control project was launched among two million people in five pilot counties of Hebei Province, near Beijing. The project was the result of collaboration between the Chinese government, the WHO and the World Bank. Cure rates of 94 per cent were achieved by the end of 1991, which encouraged the expansion of the project (TB Treatment Observer, 1996). The control programme now covers approximately half of China, with the cure rate remaining high at around 91 per cent.

A similar story of success has been reported from a DOTS programme in New York City. Following implementation of the scheme, the incidence of TB declined by 21 per cent and the number of new drug-resistant TB cases fell by 25 per cent between 1992 and 1995. The results from the New York City programme indicate that DOTS can be successful even in an area with prolific HIV and multidrug-resistant TB. Overall, DOTS programmes have been evaluated in over 20 countries, with cure rates of around 90 per cent consistently reported. This compares with cure rates of around 40 per cent for unsupervised treatment.

Despite the superior cure rates associated with DOTS, only 10 per cent of the world's TB patients are treated using this method. Lack of education among health workers and decision makers on the value of DOTS, and poorly run health services are the likely reasons for this low take-up. Cost of treatment is not a reason. Each year of healthy life saved using DOTS costs between $5 and $10, and each new infection prevented costs approximately $2 to $3, making it one of the most cost-effective health interventions available (WHO,

1995). It is the case, though, that no controlled trials have been carried out comparing DOTS with periodic health care worker monitoring of a self-medication programme.

The WHO recommends DOTS for HIV-positive TB patients (WHO, 1994). Ineffective TB treatment programmes reduce life-expectancy in nearly a third of all HIV-positive people. Studies have indicated that such patients could gain more than two years of healthy life using DOTS. An additional problem is that TB is more difficult to diagnose in an HIV-positive person. Sputum smear negative TB is more common in HIV patients. The sputum smear is likely to be less sensitive in HIV patients and some sputum smear negative (HIV-positive) people have HIV-related symptoms similar to those of TB but do not in fact have TB. Treatment of individuals with known or suspected HIV should not include thiacetazone, an inexpensive and highly effective anti-TB medicine used commonly in Africa and southern Asia, as studies in Burundi, Zaire and Zambia have indicated that its toxicity can cause fatal skin reactions (Colebunders et al, 1989; Elliott et al, 1990).

6.3 Summary

Effective medications for the treatment of TB have been available since the 1950s. Complacency combined with inadequate administration of treatment has, however, resulted in a resurgence of TB. Poor treatment practice has contributed to strains of multidrug-resistant TB developing. The threat of multidrug resistance may necessitate the development of new anti-TB medicines. It is the case, though, that currently available medicines still have the capacity to effectively treat the vast majority of TB cases.

The WHO has developed its own strategy, DOTS, to take advantage of this fact. By improving patient compliance, DOTS programmes in third-world countries have consistently recorded cure rates of around 90 per cent, more than double the success rate of previous treatment programmes. Although DOTS is perhaps most appropriate in developing countries, its aim of ensuring that patients take the required medication for the correct period of time is as relevant for the developed as the developing world, especially if the problems associated with multidrug resistance are to be minimised. The complacency which resulted from rapidly declining TB case numbers after the introduction of effective anti-TB medicines in the 1950s should not be repeated if TB is finally to be eradicated.

7 ECONOMIC ISSUES

The resurgence of TB has focused attention on the suitability of current prevention strategies and raised the question of whether governments are allocating sufficient resources to combat the disease. A 1994 WHO report noted that in 1990 only $16 million, less than one-tenth of one per cent of all the industrialised countries' foreign aid, was being devoted to TB control (WHO, 1994b). In contrast, $185 million of aid was allocated for AIDS and other sexually transmitted diseases, responsible for fewer than a quarter of the deaths due to TB. This chapter assesses the economic burden of TB and examines whether increased funding of prevention programmes provides a cost-effective use of resources. Economic implications for developed and developing countries are considered separately as the cost of TB disease management varies significantly between them.

7.1 In developing countries

Cost analysis studies carried out in developing countries have generally examined chemotherapy and case-finding, as other interventions, such as chemoprophylaxis and BCG vaccination, play a smaller role in TB control. One study examined the cost-effectiveness of chemotherapy for smear-positive TB in the national TB control programmes of Malawi, Mozambique and Tanzania (De Jonghe et al, 1994). These three countries have some of the lowest per capita incomes in the developing world. As such, estimates based on costs in these countries may not reflect costs in developing countries with higher national incomes per capita where the cost of labour is higher. Three treatment regimens were examined: short-course[19], standard[20] and retreatment[21]. The costs of programme management, laboratory services, drugs, hospitalisation and ambulatory treatment were included in the analysis. The results obtained for average incremental unit costs[22] show that one year of life can be saved from

19 Two-month intensive phase of streptomycin, rifampicin, isoniazid and pyrazinamide followed by a six-month continuation phase of isoniazid and thiacetazone.

20 Two-months of streptomycin, isoniazid and thiacetazone followed by 10 months of isoniazid and thiacetazone.

21 Two-months of streptomycin, rifampicin, isoniazid, pyrazinamide and ethambutol, followed by one-month of rifampicin, pyrazinamide and ethambutol and a five-month continuation phase of rifampicin, isoniazid and thiacetazone.

22 Variable costs plus the fixed costs attributable to the TB programme itself divided by the number of patients treated.

Table 10 **Average incremental unit costs for Malawi, Mozambique and Tanzania (US$ 1994)**

	Malawi	*Mozambique*	*Tanzania*
Short-course with hospitalisation			
Per cure	190	267	232
Per direct death averted	230	307	271
Per total death averted[a]	44	65	54
Per year of life	2.0	3.0	2.4
Standard with hospitalisation			
Per cure	247	346	310
Per direct death averted	215	313	261
Per total death averted[a]	62	87	78
Per year of life	2.8	3.9	3.6
Ambulatory short-course			
Per cure	123	93	116
Per direct death averted	149	108	134
Per total death averted[a]	29	23	26
Per year of life	1.3	1.0	1.3
Ambulatory standard			
Per cure	128	94	123
Per direct death averted	110	85	103
Per total death averted[a]	32	24	31
Per year of life	1.5	1.0	1.4

Notes:
a) Considers impact of secondary infection.
Figures have been inflated to US$ 1994 using the OECD price inflator.

Source: Adapted from De Jonghe et al, 1994.

as little as $1 (1994 prices) (see Table 10). Short-course chemotherapy has a lower cost and higher cure rate (see Chapter 6) than the standard regimen for virtually all the output indicators. This holds for hospital and ambulatory care.

The merits of short-course are further enhanced by the knowledge that fewer cases of expensive-to-treat drug resistant TB result from this form of treatment. Ambulatory chemotherapy has lower unit costs and better cost-effectiveness ratios than hospital chemotherapy (see Table 10). However, hospitalisation has been demonstrated to increase compliance and raise cure rates (Murray et al, 1991). The merits of hospitalisation are dependent on locally determined compliance levels and the marginal cost of hospitalisation.

The superior cost-effectiveness of short-course over standard

therapy was also demonstrated in a study carried out in five zonal TB centres throughout Thailand in 1987-89 (Kamolratanakul et al, 1993). All three short-course regimens examined were more cost-effective than the standard regimen. The standard regimen had a cost-effectiveness ratio (cost per sputum conversion) of $209, compared to a ratio of $70 for the most cost-effective short-course therapy. Analysis of TB treatment programmes in Indonesia showed that the short-course therapy had a cost-effectiveness ratio approximately one-quarter that of the standard-course strategy ($27.5 vs. $119 per case prevented) (Joesoef et al, 1989). Implementation of the short-course strategy in Indonesia in 1980 instead of the chosen strategy (a combination of 65 per cent standard-course and 35 per cent short-course), would have realised savings of approximately $61 million and prevented 1.8 million sputum-positive cases occurring by the year 2000.

The favourable cost-effectiveness figures reported above are reflected in the findings of the World Development Report from the World Bank (1993). This report uses the disability-adjusted life-year (DALY) for measuring the cost-effectiveness of health interventions[23]. By assessing interventions in a common currency it enables countries to target resources more appropriately at particular diseases. Forty-seven health interventions were measured which have the combined capacity to cope with over half the world's disease burden. The results presented in Figure 9 show dollar costs and gains in DALYs for all interventions measured. The axes are scaled in logarithms with the diagonal lines showing points of equal cost-effectiveness. Higher points represent more clinically effective interventions, with points further to the right representing lower-cost interventions.

Recorded cost-effectiveness ratios ranged from $1 to $10,000 per DALY gained. Chemotherapy for TB is associated with high cost but also with very high clinical effectiveness, with a consequent cost per DALY gained of approximately $2, making it one of the cheapest known health interventions applicable on a mass scale in developing countries. TB treatment costing $1 million could directly save the lives of approximately 5,000 patients and would also prevent these people from infecting others, resulting in a total gain of about 350,000 DALYs. By way of a comparison, such expenditure on diabetes management, for example, would also benefit 5,000 patients

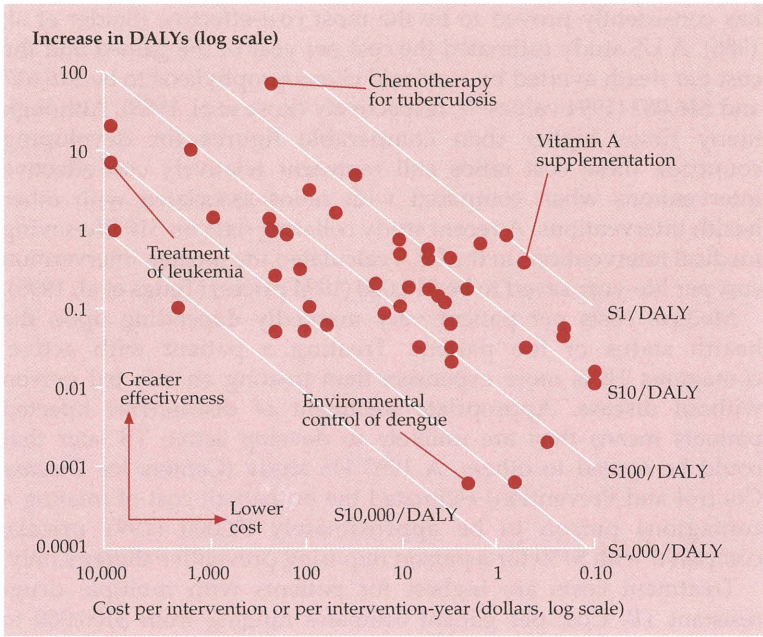
23 The present value of the future years of disability-free life lost because of premature death or disability in a given year.

but would gain only 4,000 DALYs, partly because there would be no knock-on benefit from reducing incidence (World Bank, 1993).

The numerous studies reporting favourable results with short-course chemotherapy regimens have helped the WHO to promote DOTS as a viable and cost-effective treatment strategy. Further ammunition has come from a WHO study which estimated the potential economic benefits of DOTS in India (Dholakia, 1996). This study considered: 1) improved efficiency and productivity of workers due to reduction in forced absenteeism; 2) more productive work force due to TB deaths averted; and 3) release of hospital beds. Estimates were based on two rates of TB mortality in India and real annual discount rates varying between five per cent (social time preference rate) and 16 per cent (social rate of return on capital).

The study demonstrated that DOTS is potentially highly beneficial, even at relatively high rates of discount. Even using the least favourable estimates, the potential economic benefits to the Indian economy of using DOTS are estimated at about Rs. 266 billion

Figure 9 **The cost-effectiveness of 47 health interventions**



Source: World Bank, 1993.

(US$ 8.3 billion), equivalent to about four per cent of GDP in real terms in 1993-4 . The present value of all future benefits would be as high as 66 per cent of GDP in 1993-4 (using a five per cent discount rate). The shorter the period of phasing-in DOTS, the greater will be the present discounted value of the benefits. The author calculated that even with a linear phasing-in of DOTS coverage over 10 years, with a 16 per cent discount rate, the discounted present value of all the future economic benefits of DOTS would be approximately 2.1 per cent of GDP (1993-4).

7.2 In developed countries

The cost-effectiveness of an intervention is influenced in part by the incidence, prevalence and mortality associated with the disease it is designed to combat and by the scale of costs it imposes on all parties. Health interventions, even those with a high efficacy level, tend to be less cost-effective when disease is relatively rare as more people need vaccination to prevent one case. For that reason, cost-effectiveness ratios for TB prevention interventions in developed countries are less favourable than in developing countries.

As in developing countries, the six-month 'short-course' regimen has consistently proved to be the most cost-effective (Snider et al, 1986). A US study estimated the cost per year of life gained and the cost per death averted by isoniazid chemoprophylaxis to be $16,617 and $46,082 (1994 values[24]), respectively (Rose et al, 1988). Although many times higher than comparable figures for developing countries, these cost ratios still represent relatively cost-effective interventions when compared with ratios associated with other health interventions. A recent study collating data on 310 life-saving medical interventions in the USA calculated the median intervention cost per life-year saved to be $19,000 (1994 prices) (Tengs et al, 1995).

Medical costs per patient vary markedly depending upon the health status of the patient. Treating a patient with active, contagious TB is more expensive than treating an infected person without disease. Appropriate treatment of disease-free infected patients means they are unlikely to develop active TB later that could be spread to others. A 1993 US study (Centers for Disease Control and Prevention) estimated the outpatient cost of treating a contagious person to be approximately $2,000 (1991 prices), compared with $150 for a person requiring preventive therapy only.

Treatment costs are highest for patients with multiple drug-resistant TB. Cost per patient estimates ranging from $100,000 to

24 1985 values inflated using the OECD GDP nominal price index.

$250,000 reflect the requirement for hospitalisation and a greater number of medicines (Bloom et al, 1992). The total direct medical expenditures for TB in the USA were estimated by the Centers for Disease Control and Prevention to be $703 million in 1991 (1991 dollars), with inpatient care being the most expensive item ($424m). The US General Accounting Office (1995), based on the findings of the Bloom et al study and assumptions that medical costs and TB case rates would continue to follow recent trends, estimated that total expenditures (measured in 1991 dollars) would increase to between $1.2 to $1.5 billion by 1999, approximately double the figure for 1991. The rising cost primarily reflects the increased hospitalisation that has occurred in recent years, reversing a trend apparent since sanatoria began closing in the 1950s and 1960s (Leff et al, 1993).

7.3 Cost of TB to the UK

In contrast with the US, little attempt has been made in the UK to quantify the direct medical expenditures attributable to TB. This section of the report begins to redress the balance by estimating the economic burden of the disease met by the NHS. The cost of TB to the NHS comprises four components: primary care; hospital care; pharmaceutical services and the BCG vaccination programme. The methods employed to estimate the costs of these components in fiscal year 1994/95 are described below.

Primary care

General Medical Practitioner (GP) consultation rates were obtained from the Fourth National Morbidity Survey (OPCS, 1995). This was based on data from 60 GP practices, in England and Wales, caring for a total of 502,493 patients[25]. The survey reported a consultation rate for TB (ICD 010-018) of 3 per 10,000 person years at risk. The rate increased from 1 per 10,000 for the 5-15 age group to 9 per 10,000 for the 75-84 age group. Application of age-specific consultation rates to the UK population for 1995 indicates that an estimated 17,760 GP consultations were made for TB in that year.

The Government's expenditure plans for 1997-98 to 1999-2000 estimate the average cost of a GP consultation for 1994/95 to be £9.52[26] (Department of Health, 1997). This generates an estimated

25 This is likely to underestimate TB-related consultations as TB distribution is skewed, with around 34 per cent of TB cases in England and Wales occurring in Greater London.

26 Estimate has been expressed in 1994/5 prices using GDP deflator at factor cost.

primary care cost of £169,000 for TB consultations. This relatively low figure reflects both the small number of TB sufferers in the UK and the fact that the majority of patients are not treated in a primary care setting but are instead referred to hospital-based specialists.

Hospital services

Inpatient services: Data on inpatient services are provided by the Hospital Episode Statistics (HES) and CIPFA. HES is based on a 25 per cent sample of all consultant episodes in England in a given financial year and provides information on the total number of day case admissions, ordinary admissions, and the mean length of stay for specific diseases (see Table 11). For patients with an infectious disease, CIPFA estimated the average cost per patient per day in hospital in 1994/95 (including day cases) to be £247. Applying this figure to those in Table 11 and scaling up for the total UK population gives an estimated UK NHS hospital cost of £16.39 million.

Table 11 **TB inpatient data, England, 1994/95**

	Day case admissions	*Ordinary admissions (OAs)*	*Mean duration of stay of OAs (days)*	*Total number of OA bed days*	*Total number of bed days*
TB	377	4,102	13.4	54,998	55,375

Notes:
a) A day case admission is where a patient does not require a hospital bed overnight.
b) An ordinary admission is where a patient is expected to remain in hospital for at least one night.

Source: Hospital Episode Statistics (Department of Health, 1995).

Outpatient services: Disease specific outpatient data are not recorded. In order to generate an estimate of annual outpatient costs, certain assumptions have been made. Based on advice from TB clinicians, it has been assumed that each patient consulting their GP with a TB disorder is referred to a hospital consultant and has an average of four outpatient visits and six visits from a TB-nurse during the period of their six-month standard treatment course. The average cost per infectious disease outpatient attendance at an acute hospital in 1994/95 was estimated at £96 (CIPFA). The cost of a nurse visit is estimated at £9.52. Application of age-specific patient-consulting rates, obtained from the Fourth National Morbidity Survey (OPCS, 1995), to the UK population for 1995 indicates that

9,825 patients consulted their GP[27]. Total direct costs for outpatient treatment in the UK are therefore estimated at £4.33 million [(9,825 * £96 * 4) + (9,825 * 6 * £9.52)].

Pharmaceutical services

Data on the use of pharmaceutical products comes from Prescription Cost Analysis for England, 1995 (Department of Health, 1996b). This shows that 105,800 anti-TB prescription items (BNF: 5.1.9) were dispensed in 1995. These items had an aggregate net ingredient cost (NIC) of £1.55 million. Scaling up for the UK population indicates that 126,800 prescriptions were dispensed with a NIC of £1.86 million.

Childhood Immunisation Programme (CIP)

A national scheme for childhood BCG vaccination has been operating in England and Wales since 1953. Most vaccinations are administered to children between the ages of 10 and 14, although a number of health authorities with high local incidence levels of TB operate neonatal BCG immunisation programmes. The schools programme involves a child receiving a tuberculin test and BCG immunisation if appropriate. As such, both Tuberculin Purified Protein Derivative (PPD) and BCG vaccine are used as part of the schools programme. All vaccines covered by the CIP are purchased centrally by the NHS Supplies Authority. The annual total cost for the PPD and BCG in 1994/95 was £1.80 million[28] in England and Wales (NHS Supplies Authority, personal communication). The equivalent figure scaled up for the UK would be £2.16 million.

Labour input is comprised of school doctor and nurse time taken to carry out the vaccination programme. Measurement of labour resource use specifically for the schools programme is not undertaken at a national level and so, for this analysis, estimates have been made for labour costs based on relevant salaries and time involved. From discussions with school nurse organisations it has been assumed that two three-hour sessions are required at each senior school running a vaccination programme. The first session involves three nurses carrying out skin tests. The second session involves one doctor and one nurse 'reading' the skin test and

27 The estimated 17,760 GP consultations that occurred for TB in 1995 indicates that TB patients consult their GP about that condition an average of 1.8 times per annum.

28 This includes a very small percentage sent to the Ministry of Defence.

administering the vaccine to children with a negative result. As such, twelve nurse hours and three doctor hours are required for running the programme at each secondary school, of which there were 4,462 in the UK in 1995 (Department of Education, personal communication). Based on the DoH estimation that 75 per cent of the target group of adolescents are now being immunised (see section 5.2, page 32), it is assumed that 3,346 schools participate in the programme. 'Average' hourly employment costs for school nurses and doctors have been estimated at £11.06 and £25.27 (1994/5 prices), respectively[29]. The labour cost of running the vaccination programme is estimated at £697,741 per annum [(12*£11.06*3,346) + (3*£25.27*3,346)].

The estimated total cost of the schools programme is therefore £2.86 million per annum.

Total direct costs

Aggregating the general practice, hospital, pharmaceutical and vaccination programme data indicates that the total estimated UK NHS cost of TB is £25.61 million per year (1994/5 prices) (see Table 12).

Indirect costs

An estimate of indirect costs can be made based on the number of working days lost as a result of illness caused by TB[30]. Department

Table 12 **Cost of TB to the NHS, UK, 1994/95**

Health service sector	*Cost (£ million)*
General practice	0.17
Hospital services:	
inpatient	16.39
outpatient	4.33
Pharmaceutical services	1.86
BCG vaccination programme	2.86
Total	25.61

29 School nurse employment costs based on mid-point of the salary scale for a Grade F nurse wirking 39 weeks per annum and 37 hours per week. School doctor costs based on sessional fees of medical practitioners (not consultants or specialists) undertaking part-time work in the community health service (National Pay Rates, Department of Health; personal communication).

30 This human capital approach is likely to overestimate the level of indirect costs as it measures *potential* production lost, whereas the actual loss for society may be much smaller. An alternative approach for estimating indirect costs is to use the friction cost method. The strengths and weaknesses of these two approaches are discussed in Koopmanschap et al, 1996.

of Social Security data show that the number of days in Great Britain of certified incapacity for the period 4/4/94 to 12/4/95 for TB totalled 756,000[31] (Department of Social Security, personal communication). This is based on claims for Sickness and / or Invalidity Benefit. The corresponding figure for Northern Ireland is 9,000. Such figures are likely to underestimate output loss as sickness benefit is not paid for the first three days of incapacity, and applies only to the self-employed, the unemployed and those in employment but not covered by a sickness scheme.

A monetary value can be calculated for estimated lost productivity due to TB based on lost earnings. The 1995 New Earnings Survey indicates that the average weekly salary in Great Britain in April 1995 was £336.30[32] (Office for National Statistics, 1996). The corresponding figure for Northern Ireland is £302.20. Combining these figures with the incapacity data generates an annual UK estimate for indirect costs of £42.82 million.

Burden of disease

Combining direct NHS costs with the indirect costs figure gives an estimated annual burden of TB in the UK of £68.43 million (1995 figures). The relatively high indirect costs for TB (62 per cent of total burden) reflect the lengthy periods of incapacity experienced by TB sufferers (each period of certified incapacity lasted, on average, 252 days, although this figure will be an over-estimation as periods of sickness for employed persons of less than 28 weeks are not included in the statistics). The proportion of the TB burden due to indirect costs would be even greater if a monetary valuation was given to the burden of sickness (other than lost productivity) which is felt by all sufferers and their families and friends. People aged 65+ account for approximately 35 per cent of the total number who consult their GP with TB.

The direct medical costs of TB are relatively small as treatment is medicine-based and does not involve surgery. Hospitalisation at around 66,000 bed days per annum in the UK is significant but much lower than in the era of sanitoria. Treatment is now carried out more on an outpatient basis, which is reflected in the relatively high ratio of outpatient to inpatient costs. The relatively small number of multiple-drug resistant cases has also helped to restrict the overall cost burden.

31 Based on a six day working week.

32 Based on full-time employees on adult rates, whose pay for the survey pay-period was not affected by absence.

7.4 Is there a role for the BCG vaccination in schools programme?

The level of protective efficacy of BCG vaccination of older school children (14-15 years) in Britain has remained at around 75 per cent since the schools scheme was initiated and there is no evidence to suggest it will change during the short-to-medium term (see section 5.2). However, the decline in TB notification rates that has occurred since the schools programme began in 1953 has reduced the potential benefit offered by it. For the benefit gained by the scheme is not dependent solely on the efficacy of the vaccine among tuberculin negative people. It is also dependent on the expected annual incidence of TB among tuberculin negative people if they are left unvaccinated and the proportion of the people who are tuberculin negative. Combining such data with the cost data detailed earlier would enable the cost-effectiveness of continuing the BCG vaccination programme in schools to be calculated.

Using BCG efficacy data and trends in incidence rates in England and Wales for the white population only, Sutherland et al (1989) estimated the consequences of discontinuing the scheme at various dates. Their analysis was based on two assumptions: efficacies established by the 1983 BCG survey will continue to apply in the future (80 per cent at age 15-19; 73 per cent at age 20-24; and 67 per cent at age 25-29) and notification rates will continue to decrease at a similar level to that shown since the early 1950s (nine per cent per annum for the 15-29 years age group).

The impact (and projected impact) of the scheme can be seen in Table 13, which details the estimated number of TB notifications prevented, in people aged between 15 and 30, by 100,000 BCG vaccinations of white children at about 13 years of age. These figures are derived from the difference in TB incidence rates between vaccinated and unvaccinated groups reported in the MRC vaccines trial (Hart et al, 1977). The estimated number of notifications prevented per 100,000 vaccinations declined from 1,495 in 1950 to 71 in 1979 and a projected 11 in 1999. The declining impact of the programme can also be seen with respect to the number of vaccinations required to prevent one notification, which increased from 67 in 1950 to 1,400 in 1979 and a projected 9,300 in 1999.

By combining the data detailed in Table 13 with figures on the total number of vaccinations administered per annum, Sutherland and Springett estimated the additional number of notifications that would result if the schools BCG programme was stopped (see Table 14). The increased number of notifications would consist of primary additional notifications – people left unvaccinated who would

Table 13 **Estimated number of TB notifications prevented between the ages of 15 and 30 years by the vaccination of 100,000 white schoolchildren at age 13 years in England and Wales**

Vaccinated at age 13 in:	*Notifications prevented in the 15 year period*	*Vaccinations to prevent one notification in the 15 year period*
1950	1495	67
1969	218	460
1974	106	940
1979	71	1400
1984*	45	2200
1989*	28	3600
1994*	17	5800
1999*	11	9300
*Projected		

Source: Sutherland et al, (1989).

otherwise have been protected, and secondary additional notifications – people infected by primary cases. Stopping the scheme in 1996, for example, would result in an estimated additional 25 notifications per annum by 2003 and 51 by 2013, after which the notifications would decline. The 1-5 per cent mortality rate associated with notification cases implies there could also be a number of additional deaths. However, the number of deaths among the 15-29 year age group is likely to be small as the mortality rate from TB increases markedly with age. A survey of newly notified patients with pulmonary TB in England and Wales reported that mortality among white patients was less than one per cent in the 15-34 years age group compared with 23 per cent in the 75 and over age group (Humphries et al, 1984).

The impact of stopping mass vaccination on the declining notification rates among whites aged 15-29 years would not be fully apparent until the entire 15-29 year age group had become unvaccinated. The slowing of the rate of decline following cessation of the scheme would, therefore, last for a period of about 15 years, after which it would be expected to revert to a steeper rate of decline (see Table 14).

The authors of the study concluded that the risk of an unvaccinated tuberculin-negative 13 year old developing TB has become very small in England and Wales, and is diminishing, and the probability of infection would not be greatly increased if the

Table 14 **Primary and secondary effects of stopping the schools BCG scheme at various times: estimated numbers of TB notifications at ages 15-29 years among white adults who had been resident in England and Wales at age 13 years**

		1988	*1993*	*1998*	*2003*	*2008*	*2013*
Total notifications if scheme continues		288	165	90	52	33	21
Total additional notifications (primary, secondary) resulting from							
stopping	1986	0	61(47,14)	118(71,47)	129(69,60)	95(44,51)	59(27,32)
scheme at	1991	0	0	40(31,9)	76(45,31)	82(44,38)	59(27,32)
end of:	1996	0	0	0	25(19,6)	47(28,19)	51(27,24)

Note: Some of the secondary additional notifications will be outside the age range 15-29 years.

Source: Adapted from Sutherland et al, (1989).

schools programme was terminated. The declining effectiveness of BCG was also reported in a Scottish retrospective cohort study (Capewell et al, 1997). Using the methodology of Sutherland et al, the authors estimated that stopping the schools BCG programme in 1996 would result in a maximum of 13 additional cases in 2013 in Scotland, declining thereafter.

The analysis of Sutherland et al was carried out at a time when notification rates were declining at around 8-10 per cent per year. As was reported in section 3.2, however, incidence rates have levelled out during the 1990s. Their projected numbers of notifications averted due to BCG vaccination are therefore likely to be underestimates. If it is assumed that notification rates remain at the same level as during the early 1990s, about 220 notifications would be prevented each year. With an annual programme running cost of £2.86 million this equates to a cost per notification prevented of about £13,000 (1995 prices). However, the 1993 notification survey data show that rates among whites aged 15-29, the group covered by the Sutherland et al analysis, are still declining. As such, the cost of preventing one notification in this group in 1998 will be higher, at around £24,500 (1995 prices).

In an environment of tightly constrained resources, health care providers will need to consider the viability of continuing with a

mass screening programme of 13-14 year olds. A rough guide for gauging the value for money provided by the vaccination programme can be made by comparing the cost per avoided notification with the consequent cost savings from someone not getting TB. Based on the number of notifications in 1995 and the NHS and lost productivity costs estimated in this paper (minus the cost of the vaccination programme), the estimated average cost saving per notification avoided is approximately £11,700 (£65.57m / 5,608). This estimate does not, however, take account of the quality of life 'savings' associated with an avoided notification, namely: reduced pain, anxiety and suffering.

The higher estimated cost per notification prevented compared with the estimated cost saving per notification avoided raises the issue of whether continuing with a mass screening programme is an appropriate strategy. Parallels can be drawn between the current policy debate on the appropriateness of mass BCG vaccination and the debate in the 1960s that led to the abandonment in the UK of mass radiographic screening for pulmonary TB. The decision to stop mass radiographic screening was essentially economics-based. The declining incidence of TB reduced the yield of mass radiography and caused the cost per case found to rise proportionately in real terms (Pole, 1971; Pole, 1972).

It may now be better for the UK to follow the path of other countries with low TB incidence levels, such as the USA, and carry out selective vaccination of high risk groups rather than a programme of mass vaccination. The International Union Against Tuberculosis and Lung Disease (IUATLD) has recommended that certain criteria be met before a country with low prevalence considers discontinuing a BCG vaccination programme (1994). These are:

1. the average annual notification rate of sputum smear-positive pulmonary TB should be five cases/100,000 population or less during the previous three years. **OR**:
2. the average annual notification rate of TB meningitis in children under five years of age should be less than one case per 10 million general population over the previous five years. **OR**:
3. the average annual risk of TB infection should be 0.1% or less.

The lack of an effective TB surveillance body in the UK means that we cannot collect the data necessary to determine whether the criteria laid down by the IUATLD are satisfied. Current UK notification data are cross-sectional[33] and not the required

33 Carried out at a single point in time, e.g. the Medical Research Council's notification surveys.

longitudinal[34]. However, the Department of Health are currently funding a notification survey for the whole of 1998 and it is proposed that there is a move to continuous enhanced TB epidemiological surveillance from 1999, opening up the possibility that the criteria may be shown to be met by 2004. Although the data are not currently available, many leading TB experts believe that the UK already meets the requirements of the IUATLD.

The experience of other countries, and some English district health authorities, suggests that halting a mass vaccination programme will not result in a significant increase in TB notification levels (Trnka et al, 1993; Romanus et al, 1992; Ahmed et al, 1990). Selected vaccination may be especially effective in the UK as the disease is concentrated in particular geographic areas and among certain demographic groups (see section 3.2). Specific targeting with BCG vaccine of the groups listed in Box 1 (section 5.2), except school children between the ages of 10 and 14 years, may be a more effective use of resources than the current national vaccination programme, resulting in an increased number of notifications and deaths prevented. For example, the benefit of administering BCG to infants of Asian ethnic origin born in England has been demonstrated in several case-control studies (Rodrigues et al, 1991; Packe et al, 1988). There are, however, potential ethical and political difficulties associated with a policy of targeting sub-groups of the population for preventative treatment which is not routinely made available for the rest of the population.

7.5 Summary

Chemotherapy for TB is among the most cost-effective of all health interventions for developing countries. A disability-adjusted year of life can be saved for little more than $1. The value to these countries of chemotherapy for TB is heightened by its ability to be applied on a mass scale. Such treatment can also be judged as cost-effective in western countries, where a value of $17,000 per year of life gained makes favourable reading against other health interventions in common usage. In all countries the six month short course regimen produces better cost-effectiveness results than the 12-month regimen, which is often associated with poor patient compliance.

The estimated £25.61 million spent by the UK NHS on TB in 1994/95 is relatively modest, as it represents only 0.06 per cent of

34 Continuous over time.

total NHS expenditure. This reflects the relatively small number of patients requiring hospitalisation and the fact that treatment is medicinal rather than surgical. Costs would, however, rise if the US experience of increasing numbers of multiple-drug resistant cases and greater hospitalisation were to be repeated in the UK. Indirect costs are a larger economic burden than the direct health service expenditures. The estimated £42.82 million of such costs attributable to TB represents nearly two-thirds of the total cost of the disease. This is mainly a result of the lengthy periods of incapacity experienced by TB sufferers.

The annual cost of running the BCG vaccination in schools programme is estimated at £2.86 million. This equates to a cost per notification prevented of about £13,000[35] (1994/5 prices) based on current prevalence rates. If TB cases were to decline in future at the same rate as prevailed prior to the 'levelling-out' period of the early 1990s, then the cost per primary notification prevented could rise to about £87,000 (1994/5 prices) by 2013. Even at current incidence levels, the relatively high cost per notification prevented makes the value of vaccinating all children by age 14 questionable and has prompted some health authorities to discontinue such a policy. A selective vaccination policy is likely to be more cost-effective, targeting specific sub-sets of the population who are known to have higher prevalence rates. A cost-benefit study is required to assess the full economic, epidemiological and quality of life implications of various vaccination strategies, including a policy of no vaccination.

35 This figure is based on primary notifications prevented. The cost ratio would be slightly lower if secondary notifications (people infected by a primary notification) were also included.

8 SUMMARY AND CONCLUSIONS

This paper has highlighted the global problem presented by TB, as well as focusing attention on its re-emergence in the UK. Approximately one-third of the world's population is infected with *Mycobacterium tuberculosis*, with a further eight million developing clinical disease annually. TB now kills around three million people each year, more than any other infectious disease, with South-East Asia and Africa the worst affected regions. The TB epidemic has been fuelled by the rise in HIV incidence levels, as HIV weakens a patient's immune system making it less able to ward off the growth and spread of *Mycobacterium tuberculosis*. HIV has had a particularly large impact in Africa, where it is estimated that around 30 per cent of TB cases will be attributable to it by 2000.

TB is not only a third world issue, however. Increasing notification rates have been recorded in industrialised countries. TB rates in the UK increased during the early 1990s after a period of almost uninterrupted decline throughout the century. The reported increase was concentrated among certain ethnic groups, particularly those from the Indian sub-continent group and amongst those living in the inner cities. High TB prevalence in the Indian subcontinent and Africa and poor social conditions are, therefore, the most likely reasons for this recent increase. HIV has not had the same impact in the UK as in Africa or, indeed, as in certain other industrialised countries.

The rising global TB mortality and incidence levels are a particular indictment, as the medications to treat and ultimately eradicate the disease have been available since the 1950s. The belief that TB was a disease of declining significance appears to have led to a degree of complacency in disease management among western countries, perhaps heightened by the fact that TB has, for the latter part of this century, been predominantly a third world disease.

Such complacency is especially hard to excuse in view of the high cost-effectiveness of TB chemotherapy treatment. Six-month short-course therapy costs only one or two dollars per life-year saved in many developing countries, making it one of the most cost-effective of all health care interventions applicable on a mass scale. This is one factor driving the WHO's efforts to get directly-observed treatment, short-course (DOTS) programmes operating in all countries. Currently only 10 per cent of TB patients are treated using DOTS. Even in western countries, six-month short-course therapy offers a relatively high level of cost-effectiveness, around $17,000 per year of life saved, in comparison with other commonly used health

interventions. A further economic incentive to treat patients 'correctly' is that inadequate treatment, often due to poor patient compliance, leads to multiple-drug resistant TB which is up to 100 times more expensive to treat than the non-drug-resistant strains.

The estimated £26 million spent annually by the NHS on TB treatment and prevention represents a small proportion of total NHS expenditure. This reflects the relatively small number of patients requiring hospitalisation and the fact that treatment is medicinal and not surgical. Expensive-to-treat drug-resistant cases in the UK are currently very rare, although there have been increasing numbers during the last two to three years. Increasing cases of drug-resistance are one reason why US direct medical expenditure on TB is predicted to double from its 1991 level of $700 million to around $1.4 billion in 1999 (1991 prices).

The value of continuing a mass BCG vaccination programme in the UK is now a matter of debate. The efficacy of BCG is not in question, with protective efficacy rates around 75 per cent consistently recorded. However, the changing epidemiology associated with TB means that the mass vaccination programme prevents fewer notifications than has historically been the case. A relatively high ratio for cost per notification prevented of about £13,000 (1995 prices) has been estimated, and an even more unfavourable ratio would be noted if applied to the white population only. This is counter-balanced by a cost saving per notification prevented of similar magnitude (£11,700) and by the avoidance of pain and distress for the (relatively few) people who would otherwise contract TB.

A more cost-effective approach may be achieved if the UK follows the example of other countries with low TB incidence levels and undertakes selective screening of high risk groups rather than a mass vaccination policy. Such an approach may be particularly appropriate for the UK as the disease is concentrated among certain demographic groups and in particular geographic regions. Prevention techniques still have a role to play alongside treatment in combating TB but, perhaps, in a selective way.

TB is a disease associated with widespread morbidity and mortality, but a disease we have the ability to treat effectively and, ultimately, eradicate. If TB is to be eradicated, the lessons of the second half of the twentieth century need to be learned. TB should be considered a global problem and not 'just' a third world issue. Control programmes in developing countries will need sufficient financing to restrict the TB epidemic there and to help combat the spread of disease to other countries.

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