

Tuberculosis

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Tuberculosis is an ancient disease that has long been a significant public health challenge in the world and remains a significant health problem in developing countries. In the last century, tuberculosis was responsible for nearly one in ten deaths in Europe (Preston, Keyfitz, and Schoen 1972). There is reliable evidence that irrespective of its magnitude, the tuberculosis problem in industrial countries has been decreasing for at least the last forty years, since the introduction of antituberculosis chemotherapy. In many industrial countries, a steady decrease in mortality from tuberculosis in the pre-chemotherapy era was observed from the turn of this century if not before (Frost 1937; Styblo 1986). The elimination of tuberculosis in most industrial countries will not be substantially influenced by acquired immunodeficiency syndrome (AIDS) because of the low prevalence of tuberculous infection in subjects age twenty to fifty years in whom infection from the human immunodeficiency virus (HIV) is most frequent (Styblo 1989). In developing countries, however, tuberculosis continues to be an important problem and there appears to have been virtually no tendency for tuberculosis to eliminate itself in the absence of intensive control measures. Unlike in industrial countries, HIV infection will result in a considerable increase of tuberculosis cases in those developing countries where both tuberculous and HIV infections are prevalent. Tuberculosis remains, therefore, one of the top priorities for action in developing countries, because tools exist to diagnose and cure infectious cases of tuberculosis and thus to decrease transmission of tuberculous infection.

The epidemiology of tuberculosis is complex and a certain knowledge of the natural history of tuberculosis is required in order to discuss the policy options. Tuberculosis is caused by the bacillus *Mycobacterium tuberculosis*, which in most cases attacks the lungs. Infection is most commonly transmitted from persons with pulmonary tuberculosis to other persons, in particular when coughing or sneezing. The most important exception to the airborne route of infection is infection of the digestive tract through contaminated milk containing *Mycobacterium bovis* from cows suffering from tuberculosis, which causes a disease clinically similar to tuberculosis.

One or more bacilli reaching the lung tissue can cause a nonspecific inflammatory response, which may result in a

primary complex. The primary complex has two components, one in the lung and the other in the corresponding lymph node or nodes. In most cases, both the primary pulmonary lesions and lesions in lymph nodes heal spontaneously, leaving behind a focus of a few "dormant" bacilli that can be reactivated and cause clinical disease at any moment during an individual's lifetime. Before the development of allergy and immunity, some bacilli escape from the primary lesions into the blood stream and set up blood-borne foci in other parts of the body, for example, in the kidneys, ends of long bones, spine, or brain. In newborns and small children the infection progresses either in the primary site or metastatic foci, and serious forms of tuberculosis may develop, in particular, miliary tuberculosis and tuberculous meningitis. These forms of tuberculosis also occur in adolescents and adults but much less frequently than in newborns and small children.

Two to six weeks after the primary infection, the body's immune system develops a certain level of cell-mediated immunity to *M. tuberculosis* antigens. This leads to the formation of granulomas—a type of histological pattern—around the focus of the bacilli. When these areas become calcified, they may be detected on a chest x-ray as a calcified primary complex. (If the calcified lesions of the primary complex in the lung and the lymph node are too small, they may not be seen on an x-ray.) Clinical disease, however, may occur weeks to years after the primary infection with the bacillus, although about 80 percent of all cases occur during the first two years after infection (Sutherland 1968). The probability of progressing from a primary infection to clinical tuberculosis is discussed more fully below. The key aspect of the natural history of tuberculosis is that infection may lead, in a relatively small proportion of infected persons, to clinical disease at a later date. Consequently, the process of elimination of tuberculosis in a community is very slow, because a certain risk of latent infections developing into active tuberculosis (endogenous exacerbation) cannot be completely prevented.

Four important diagnostic strategies are used to detect tuberculous infection and clinical disease. First, a recently or remotely infected person, whether or not he or she has clinical disease, develops a certain degree of cell-mediated immune response to *M. tuberculosis* antigen. An intradermal injection

of tuberculin (preferably purified protein derivative) will cause an induration in forty-eight to seventy-two hours. This skin test (Mantoux test) permits a relatively easy detection of the prevalence of tuberculous infection in any population. The tuberculin test does not distinguish, however, between recent and remote infections or between an infection caused by *M. tuberculosis* and one caused by *M. bovis* or by some other mycobacteria. In spite of these limitations, tuberculin sensitivity surveys in a representative sample of a population are one of the mainstays of tuberculosis epidemiology. The tuberculin test, however, has a limited value for the diagnosis of clinical tuberculosis. If the test is positive, it does not distinguish between infection and disease; if it is negative it does not always exclude disease. Studies by Canetti (1939, 1972) indicate that most patients who have been infected and have a positive skin test maintain viable bacilli within their bodies.

Second, detection by microscopy of acid-fast bacilli (nearly always identical with tubercle bacilli) in sputum and other specimens (for example, gastric washings) is the most important tool to detect highly infectious cases of tuberculosis. There is strong evidence (Rouillon, Perdrizet, and Parrot 1976; Styblo 1984) that those patients whose sputa contain sufficient bacilli to be detected by microscopy are highly infectious. These cases are referred to as "smear-positive."

Third, the culture of specimens for mycobacteria detects, in about four to six weeks, tubercle bacilli in sputum containing insufficient bacilli to be detected by microscopy. These cases are then classified as sputum smear-negative but "culture-positive" pulmonary tuberculosis. Patients whose sputum is smear-negative and culture-positive or culture-negative are several times less infectious than smear-positive cases.

Fourth, in smear- and culture-negative patients (particularly in children and young adults) diagnosis of tuberculosis is made on the basis of clinical examination and interpretation of chest x-ray.

Extrapulmonary tuberculosis is diagnosed by, in a number of cases, bacteriology (in patients with tuberculous meningitis, lymphadenitis, genitourinary tuberculosis, and the like) or by histology of biopsy material. Depending on the site of infection, roentgenologic and other special examinations are required to diagnose extrapulmonary tuberculosis. It is important to stress that extrapulmonary tuberculosis is either noninfectious or the degree of infectivity is very low.

The natural history of tuberculosis illustrates that patients suffering from smear-positive pulmonary tuberculosis are the main source of infection. For the rest of this chapter, therefore, tuberculosis will be divided into two categories: (a) sputum smear-positive tuberculosis, which will be referred to as smear-positive tuberculosis; and (b) other tuberculosis, which includes pulmonary tuberculosis, in which the sputum is smear negative, and extrapulmonary tuberculosis. Because children rarely suffer from sputum smear-positive tuberculosis, most cases of tuberculosis in children will be included in the category "other tuberculosis." (If children are smear positive, they are highly infectious sources of infection. If they are smear negative and culture positive or smear negative and culture

negative they are much less infectious.) The above two categories are sometimes labeled infectious or open tuberculosis and noninfectious tuberculosis, respectively (India, Ministry of Health and Family Welfare 1986). The distinction between sputum smear-positive tuberculosis and other tuberculosis is particularly important when considering the policy options for tuberculosis control and prevention.

Tuberculosis without detection and the institution of adequate treatment is highly fatal—specific studies will be reviewed below. Because mycobacteria are able to survive within host lesions as persisters (dormant bacilli), treatment is long and requires, in smear-positive cases, the combination of at least two drugs in the initial intensive phase. Length of treatment ranges from six to eighteen months.

Tuberculosis Incidence and Mortality

In the following section, we outline the empirical and epidemiological basis for estimating tuberculosis incidence and mortality.

Tuberculosis Incidence

To put tuberculosis in the proper perspective we need to know the number and the age distribution in new cases of tuberculosis which develop in a community each year, as well as the number and the age distribution of patients who die from tuberculosis each year. Health information systems in developing countries are too incomplete to provide meaningful information on the incidence or mortality of tuberculosis (Styblo and Rouillon 1981). We are forced to estimate the burden of tuberculosis indirectly by using several epidemiological parameters. These include the average annual risk of tuberculous infection and the incidence of smear-positive pulmonary tuberculosis, the proportion of all cases of tuberculosis that are smear positive, and case-fatality rates for smear-positive tuberculosis and other tuberculosis.

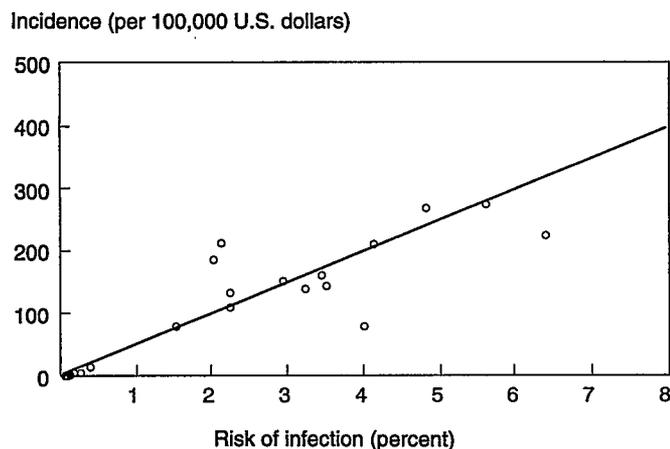
ANNUAL AVERAGE RISK OF TUBERCULOUS INFECTION. Tuberculosis epidemiologists have used skin tests to measure the prevalence of infection in communities. A technique has been developed for converting this information on prevalence of

Table 11-1. Estimated Risks of Tuberculosis Infection in Developing Countries 1985–90
(percent)

Area	Risk of infection	Annual decrease in risk
Sub-Saharan Africa	1.50–2.50	1–2
North Africa and western Asia	0.50–1.50	4–5
Asia	1.00–2.00	1–3
South America	0.50–1.50	2–5
Central America and the Caribbean	0.50–1.50	1–3

Source: Based on Cauthen, Pio, and ten Dam 1988.

Figure 11-1. Relationship between Annual Risk of Infection and Incidence of Smear-Positive Tuberculosis



Source: Authors.

tuberculous infection into a series of annual risks of tuberculous infection (Styblo, Meijer, and Sutherland 1969; Sutherland 1976). If several tuberculin surveys of the same population have been made at different times (using similar techniques and testing a representative sample of subjects of the same age not vaccinated with BCG [bacille Calmette-Guérin]), the level of and percentage decrease in the risk of infection can be estimated. Techniques have been developed to estimate, if the pattern of the annual risk of infection by age is assumed, the level and time trend in the annual risk of infection from a single tuberculin survey (Sutherland 1976). The annual risk of infection tells us the probability that any individual will be infected or reinfected with *M. tuberculosis* in one year. This measure has become the standard indicator of the tuberculosis burden in a community (Leowski 1988).

Since the 1950s many different tuberculin sensitivity surveys in developing countries have provided us with an approximate picture of the annual risk of infection in different regions of the developing world. Our best estimates, based on a recent review of survey data on the annual risk of infection, are presented in table 11-1. The annual risk of tuberculous infection is probably highest in Sub-Saharan Africa, followed closely by Asia. For comparison the annual risk of infection in the Netherlands in 1985 was 0.012 percent (Styblo 1989).

INCIDENCE OF SMEAR-POSITIVE TUBERCULOSIS. Incidence of smear-positive pulmonary tuberculosis is one of the two key epidemiological indexes (the other being the average annual risk of tuberculous infection) for evaluation of the overall tuberculosis situation. Lack of data on smear-positive tuberculosis cases in developing countries makes it difficult to convey the enormity of the tuberculosis problem to the public health community. It is not possible readily to obtain reliable information on incidence of smear-positive tuberculosis in developing countries because case-

detection rates can be only a fraction of the respective true incidence rates.

Prevalence of smear-positive cases is of limited value as an epidemiological index because it largely depends on the quality of chemotherapy of smear-positive cases and the extent and quality of case finding. (In industrial countries, prevalence may be substantially lower than incidence, especially in countries where a six-month course of treatment is given to patients. In developing countries, prevalence may be several times higher than incidence if treatment results are poor and the case-detection rate is low.) For these very same reasons, prevalence may be an important indicator for management of a national tuberculosis control program, but estimates of prevalence depend on too many locally specific parameters to be made here for regions or for the developing world as a whole.

The relationship between the annual risk of infection and the incidence of smear-positive tuberculosis can provide one of the only means of estimating the incidence of smear-positive tuberculosis (Styblo 1985). Styblo examined the relationship between the annual risk of infection and incidence of smear-positive pulmonary tuberculosis using a variety of data sources from the developing and industrial world. We have recomputed this relationship using only the results of a series of surveys sponsored by the World Health Organization in developing countries and data from the Netherlands before chemotherapy was widely available. We must note that for some of these surveys data are available on the prevalence of smear-positive tuberculosis, not the incidence. In such cases, we derived the incidence rates by using the historical observation that the prevalence of smear-positive tuberculosis was usually twice the incidence in the communities without widespread institution of chemotherapy (Holm 1970). In these developing countries, the relationship between the annual risk of infection and incidence of pulmonary smear-positive tuberculosis was linear. A least squares regression line (figure 11-1) gives an

Table 11-2. Estimated Incidence of Smear-Positive Tuberculosis in Developing Countries, 1985-90

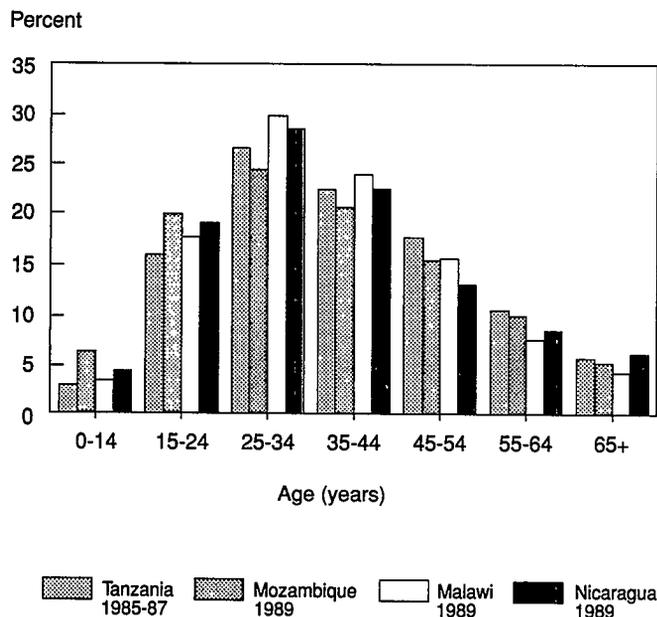
Area	Cases			Incidence (per 100,000)
	Low	Midpoint	High	
Sub-Saharan Africa ^a	342,921	591,445	839,970	117
North Africa and western Asia	52,592	145,640	238,687	54
Asia	1,141,877	2,298,393	3,454,909	79
South America	57,937	160,440	262,943	54
Central America and the Caribbean	30,022	83,138	136,266	54
Total	1,625,349	3,279,056	4,932,775	79

Note: Based on annual risk of infection for each region presented in table 11-1, 1990 population, and incidence of thirty-nine to fifty-nine cases per 100,000 population for each 1 percent annual risk of infection.

a. Includes cases attributable to dual HIV/tuberculosis infections.

Source: Authors.

Figure 11-2. Age Distribution of Smear-Positive Tuberculosis in Four Sub-Saharan Tuberculosis Programs



Source: Tanzania: Chum and others 1988; other countries: government registry data.

estimate of 49 cases of smear-positive tuberculosis per 100,000 for every 1 percent annual risk of infection. The 95 percent confidence interval for the coefficient is 39 to 59.¹

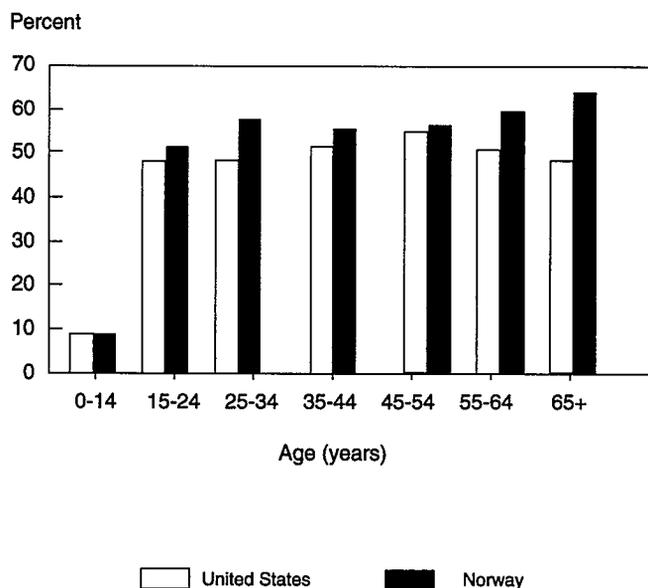
Using the estimates of the risk of infection for different regions in table 11-1 and the confidence interval for the relationship between incidence of pulmonary smear-positive tuberculosis and the risk of infection, we have calculated the low and high estimates of the incidence of smear-positive tuberculosis for different regions (table 11-2). The midpoint of the confidence interval of the estimates of smear-positive incidence is 3,208,000 cases, or an incidence of 77 per 100,000 in the developing world. These must be viewed as only crude estimates, which nevertheless illustrate the continuing magnitude of the tuberculosis problem.

AGE DISTRIBUTION OF SMEAR-POSITIVE TUBERCULOSIS. The age distribution of incidence is important in determining the effect on public health of smear-positive tuberculosis and the most appropriate means of preventing or controlling tuberculosis. From the historical record of industrial countries and epidemiological models, the age and sex distribution of incidence appears to change as the annual risk of infection declines. Because most developing countries have annual risks of tuberculous infection between 1 and 2 percent, we propose to use the age distribution of the incidence of smear-positive tuberculosis from a developing country with an annual risk of infection in this range. There is no reason to believe that the epidemiology and thus the age distribution of incidence for a

given annual risk of infection will vary substantially between communities. Because the tuberculosis control program in Tanzania is well organized and captures most of the tuberculosis cases, the age distribution from Tanzania will be used as representative of the developing world. In figure 11-2 we show the age distribution of smear-positive tuberculosis in Tanzania for 1985-87 (Chum and others 1988), Malawi for 1989, Mozambique for 1989, and Benin for 1989. The pattern is remarkably similar in these four countries, all of which have good programs and case registration. It is important to note that BCG coverage in Tanzania was roughly 50 percent in 1983-87 (Bleiker and others 1987), based on scar examination in the National Tuberculin Survey in Tanzania carried out on 80,000 schoolchildren from twenty regions selected at random from 1983 to 1987, which is below the officially reported average for the developing world (UNICEF 1988). Thus any effect such BCG coverage may have on preventing tuberculosis in children is partially represented in the age distribution; because world coverage is probably higher than in Tanzania, the estimate for the incidence of smear-positive tuberculosis in children based on this age distribution may be slightly high. Clearly, smear-positive cases are relatively rare in children; smear-positive tuberculosis is concentrated in adults—more than 80 percent of cases occur between the ages of fifteen and fifty-four, according to the data from these four countries.

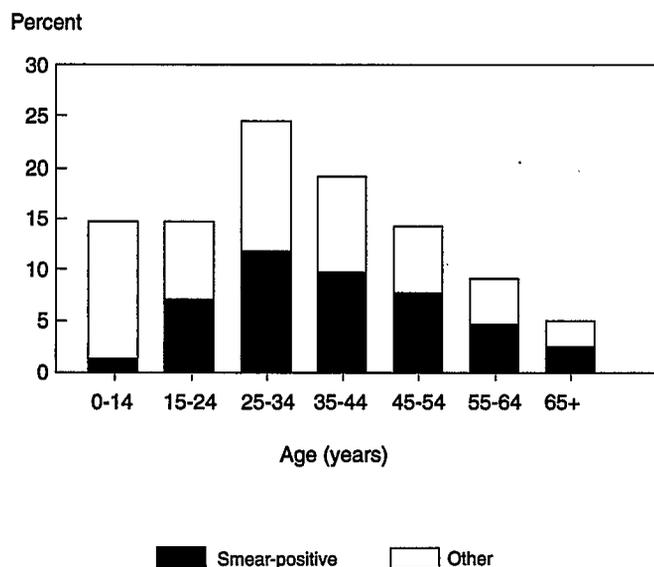
INCIDENCE OF OTHER FORMS OF TUBERCULOSIS. Estimates of the incidence of smear-negative pulmonary and extrapulmonary

Figure 11-3. Smear-Positive Tuberculosis as a Proportion of All Cases of Tuberculosis, by Age, United States (1985-87) and Norway (1951-72)



Source: United States: CDC (unpublished data); Norway: Tuberculosis Surveillance Research Unit (TSRU; unpublished data).

Figure 11-4. Estimated Age Distribution of Tuberculosis in the Developing World, 1990



Source: Authors.

tuberculosis are also needed. These forms of tuberculosis are particularly difficult to quantify because the main diagnostic tool used in developing countries, sputum microscopy, does not detect these cases. Because the diagnosis of extrapulmonary tuberculosis is often based on clinical criteria, no survey data are available to estimate the relation between the risk of infection and other tuberculosis. In the past, estimates of smear-positive tuberculosis have simply been doubled to provide a figure for other tuberculosis (Styblo and Rouillon 1981; Leowski 1988). The distribution of total cases between the categories sputum smear-positive and other tuberculosis cannot be accurately established. Whereas smear-positive tuberculosis and tuberculosis positive by culture can be objectively determined, the number of culture-negative cases detected depends on various factors, such as whether or not mass miniature radiography is used to find cases (this method was extensively employed in Europe in the 1950s, 1960s, and 1970s), the criteria used for activity in asymptomatic cases, age group, and so on. We will assume that within each age group, using the same diagnostic approach, the percentage of cases that are sputum smear-positive and the percentage of other cases should be the same independently of the overall annual risk of infection. The proportion of all tuberculosis cases in the United States and Norway that are smear-positive by age is shown in figure 11-3 (Galtung Hansen 1955; and personal communication from the Centers for Disease Control in Atlanta (CDC) in 1989). Because the data set for the United States is larger and no mass miniature radiography was used on a large scale, we will use the ratio of cases of other tuberculosis to smear-positive tuberculosis within each age group in the United States. Using the age distribution of the incidence of

smear-positive tuberculosis in Tanzania and the age-specific ratios of other to smear-positive in the United States, we have derived the rough estimate of the age distribution of other tuberculosis shown in figure 11-4. Although the assumptions underlying these estimates of other tuberculosis may be challenged on many grounds, we believe it is preferable to make some objective attempt to estimate the age distribution of smear-negative and extrapulmonary tuberculosis in developing countries because it is an important input to policy decisions.

Our estimations imply that there are 1.22 cases of smear-negative and extrapulmonary tuberculosis for every case of smear-positive tuberculosis in developing countries with an annual risk of infection between 1 and 2 percent and an overall age distribution similar to Tanzania. Low and high estimates of the number of new cases of smear-negative and extrapulmonary tuberculosis for each region in the developing world are provided in table 11-3. For all types of tuberculosis combined, the data in table 11-4 indicate that the incidence of tuberculosis exceeds 260 per 100,000 in Sub-Saharan Africa.

HIV-ASSOCIATED TUBERCULOSIS INCIDENCE. The close relationship between HIV infection and clinical tuberculosis that has been widely observed will substantially affect the predicted incidence of clinical tuberculosis in regions with high levels of HIV seropositivity. Using the most recent estimates of country-specific seroprevalence provided by the World Health Organization, we estimate that there are approximately 4.9 million HIV-seropositive patients in Sub-Saharan Africa. Using estimates of the prevalence of tuberculosis infection in the region, we arrive at the approximate figure of 2.1 million cases of dual HIV and tuberculosis infections. Individuals with dual infections have much higher rates of breakdown from infection to clinical disease (Selwyn and others 1989). A range for the annual breakdown rate in dually infected individuals of 5 to 10 percent has been used to estimate that an additional 105,000 to 210,000 cases of tuberculosis occur each year in Sub-Saharan Africa. These extra cases have been included in tables 11-2 through 11-6. If seroprevalence continues to rise, the tuberculosis burden attributable to the HIV epidemic will also rise. For the estimates in this chapter, we assume the same clinical spectrum between smear-positive and other tuberculosis for HIV-positive patients (Chaisson and Slutkin 1989).

Tuberculosis Mortality

This section discusses death rates of tuberculosis and their age distribution.

CASE-FATALITY RATES. In order to calculate tuberculosis mortality from the estimates of incidence derived above, we need to estimate the case-fatality rate. Without appropriate chemotherapy, tuberculosis is highly fatal. Two types of sources provide information on the relationship between incidence and tuberculosis mortality: data from before chemotherapy was available in industrial countries and survey data from southern India. First, Drolet (1938) investigated the relation between

Table 11-3. Estimated Incidence of Other Forms of Tuberculosis in Developing Countries, 1990

Area	Cases			Incidence (per 100,000)
	Low	Midpoint	High	
Sub-Saharan Africa ^a	418,363	721,563	1,024,763	143
North Africa and western Asia	64,162	177,680	291,198	66
Asia	1,393,090	2,804,039	4,214,989	96
South America	70,683	195,737	320,791	66
Central America and the Caribbean	36,627	101,429	166,231	66
Total	1,982,925	4,000,448	6,017,972	96

Note: Based on the relationship between smear-positive tuberculosis and other forms of tuberculosis in the United States by age, combined with the age distribution of smear-positive tuberculosis in Tanzania.

a. Includes cases attributable to dual HIV/tuberculosis infections.

Source: Authors.

the tuberculosis mortality rate and reported incidence in selected American cities from 1915 to 1935. He found that the estimated case-fatality rate for all types of tuberculosis in Detroit and New Jersey was 58.8 percent and 54.9 percent, respectively. The calculated case-fatality rate varied little during that twenty-year period. Similar case-fatality rates for all forms of tuberculosis were recorded in European countries—Denmark, 1925–34: 51.2 percent (Lindhart 1939); Norway, 1925–44: 50.6 percent (Galtung Hansen 1955); and England and Wales, 1933–35: 49.1 percent (Drolet 1938). The most detailed study is from Berg (1939), who followed 6,162 smear-positive patients for periods of up to twenty years. After two years, 40.1 percent had died; deaths increased to 60.7 percent

Table 11-4. Estimated Incidence of All Forms of Tuberculosis in Developing Countries, 1990

Area	Cases			Incidence (per 100,000)
	Low	Midpoint	High	
Sub-Saharan Africa ^a	761,284	1,313,008	1,864,733	260
North Africa and western Asia	116,754	323,320	529,885	120
Asia	2,534,966	5,102,432	7,669,898	174
South America	128,619	356,177	583,734	120
Central America and the Caribbean	66,649	184,567	392,485	120
Total	3,608,272	7,279,504	10,950,735	175

Note: Based on annual risk of infection for each region presented in table 11-1, 1990 population, and incidence of thirty-nine to fifty-nine cases per 100,000 population for each 1 percent annual risk of infection and also the relationship between smear-positive tuberculosis and other forms of tuberculosis in the United States by age, combined with the age distribution of smear-positive tuberculosis in Tanzania.

a. Includes cases attributable to dual HIV/tuberculosis infections.

Source: Authors.

Table 11-5. Estimated Cases of Tuberculosis Detected and Case-Fatality Rates in Developing Countries, 1990

Area	Cases detected	Percentage of total cases actually detected	Case-fatality rates ^a (percent)	
			Low	High
Sub-Saharan Africa	325,132	25	39	47
North Africa and western Asia	222,686	69	26	29
Asia	2,572,809	50	32	37
South America	221,856	62	28	32
Central America and the Caribbean	62,054	34	38	45
Total	3,404,537	47	33	38

Note: Based on assumption that 15 percent of patients receiving standard chemotherapy die; this is a conservative assumption.

Source: Authors.

at five years and 73.3 percent at ten years. Berg found that even fifteen to nineteen years after diagnosis, smear-positive patients had mortality rates five times higher than the general population of the same age. Second, a five-year study of the natural history of tuberculosis in Bangalore, India, found that 49 percent of smear-positive and culture-positive patients whose tuberculosis was detected on the first round of the survey were dead within five years (Olakowski 1973; National Tuberculosis Institute, Bangalore 1974). Mortality was concentrated in the first year and a half, during which 30 percent of the patients died. The death rate among new cases dropped in the second and third rounds (32.4 percent over three and one-half years in the first round and 33.9 percent over two years in the second round) because all round 2 patients received isoniazid for one month. Taken together, these data suggest that, without treatment, from 50 to 60 percent of tuberculosis patients will die.

The case-fatality rate for smear-positive patients is thought to be higher than for all forms of tuberculosis combined. Rutledge and Crouch (1919) followed 1,229 patients who had smear-positive tuberculosis and found that 66 percent of them were dead within four years. Lindhart (1939) found in Denmark that 66 percent of patients who were bacteriologically positive died. Berg's results for smear-positive patients provide the most direct evidence on the higher case-fatality rate of smear-positive tuberculosis. A higher mortality of smear-positive patients has also been shown in the study in southern India (Olakowski 1973). Of the 126 bacillary patients detected in round 1, the death rate in the culture-positive and smear-negative group (62 patients) was 45.2 percent at five years and 53.1 percent in the smear-positive group (64 patients) for the same period. Case-fatality rates must also be expected to vary between communities as a result of other factors, such as nutrition and concurrent infections. Still, the above studies provide a rough indication of the likely range in case-fatality rates from tuberculosis. If the case-fatality rate for smear-

positive tuberculosis is higher than for all forms of tuberculosis, then the case-fatality rate of other tuberculosis on average must be somewhat lower. In other tuberculosis, however, some forms, such as tuberculous meningitis, will cause 100 percent or very high case-fatality rates if the patients receive no treatment. For the rest of this chapter, we will assume that the case-fatality rate for smear-positive tuberculosis is 60 to 70 percent; for other tuberculosis as a whole, 40 to 50 percent; and for all forms combined, 50 to 60 percent.

TUBERCULOSIS DEATH RATES IN DEVELOPING COUNTRIES. The tuberculosis death rates in developing countries cannot be as high as the incidence rates and a case-fatality rate of 50 to 60 percent imply, because a significant proportion of cases are detected by existing health services and the patients receive treatment. For all those cases that are estimated to be detected and receive treatment, we assume the case-fatality rate is reduced to 15 percent after five years. For example, in the East African and British Medical Research Council survey in Kenya the case-fatality rate for patients receiving standard chemotherapy was 13 percent after twelve months (East African and British Medical Research Council 1977, 1979). In many countries, however, the case-fatality rate may be over 15 percent for those receiving chemotherapy, after five years of follow-up, making the following estimates of mortality conservative.

Estimates of the percentage of new cases that are detected and the patients treated are based on the number of cases of tuberculosis detected that are reported by countries to the World Health Organization (table 11-5; WHO 1988). Because reporting is extremely variable, these estimates are based on the highest number of cases reported by each country for any year in the last decade. This basis is justified by the assumption that year-to-year variation in the number of cases reported, which can be greater than an order of magnitude, is due more to incomplete reporting of health service activities than to changes in the epidemiology of tuberculosis. The number of new cases reported from some programs has been confused with the total number registered at the end of the year, which includes old cases. We have adjusted the country estimates for

Table 11-6. Estimated Incidence of All Forms of Tuberculosis in Developing Countries, 1990

Area	Cases			Incidence (per 100,000)
	Low	Midpoint	High	
Sub-Saharan Africa ^a	300,604	585,591	870,578	116
North Africa and western Asia	29,881	90,960	152,039	34
Asia	811,303	1,824,756	2,838,208	62
South America	35,915	110,548	185,180	37
Central America and the Caribbean	25,217	79,966	134,715	52
Total	1,202,920	2,691,820	4,180,720	65

a. Includes deaths attributable to dual HIV/tuberculosis infections.

Source: Authors.

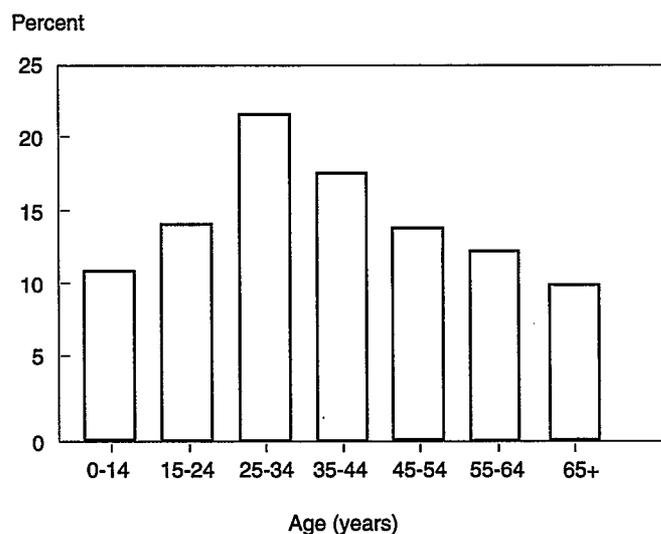
specific countries to reflect newly registered cases.² In addition, the highest number of cases reported in the last ten years has been adjusted upward by 20 percent for those regions with an active private sector to try to account for those cases that are detected in the private sector but are not reported to the government; in Asia, where data for some large countries may include a large number of retreatment cases, we have not adjusted the figures by 20 percent.

Separate estimates for the percentages of smear-positive and other cases are needed. The primary mode of case detection varies across regions; for example, in Sub-Saharan Africa, sputum microscopy is the main tool, whereas in China, much greater emphasis is placed on chest radiography. We will assume arbitrarily that 50 percent of cases detected are smear positive and 50 percent are other tuberculosis. This mix between smear-positive and other tuberculosis cases is probably an underestimate for Sub-Saharan Africa and an overestimate for Asia. The detection rate of the various forms of tuberculosis and the likely range of case-fatality rates discussed above can be combined to estimate the tuberculosis death rates from smear-positive tuberculosis and other tuberculosis.

In table 11-6 we show estimated deaths each year from all forms of tuberculosis based on the calculations of the tuberculosis death rates discussed above. The wide confidence intervals reflect the cumulative uncertainty in the parameters of the estimation procedure. The midpoints of the confidence intervals give a total number of deaths from tuberculosis in the developing world of almost 2.7 million. Tuberculosis, therefore, accounted for approximately 6.9 percent of all deaths in the developing world in 1990 (United Nations 1986).³

AGE DISTRIBUTION OF TUBERCULOSIS DEATHS. To estimate the age distribution of tuberculosis deaths, we must take into

Figure 11-5. Estimated Distribution of Deaths from Tuberculosis in the Developing World, 1990



Source: Authors.

Table 11-7. Distribution of Tuberculosis Deaths by Age in Three European Countries before the Availability of Anti-Tuberculosis Chemotherapy (percent)

Age (years)	Czechoslovakia			Norway			Netherlands			
	1940	1931	1941	1951	1931	1941	1951	1931	1941	1951
0-14	11.7	11.8	10.3	8.0	24.0	19.4	13.6	24.0	19.4	13.6
15-24	22.0	30.6	25.4	10.8	22.4	20.3	12.8	22.4	20.3	12.8
25-34	18.7	25.9	25.4	24.4	20.8	20.7	16.9	20.8	20.7	16.9
35-44	14.0	14.5	9.6	13.2	11.7	13.1	12.8	11.7	13.1	12.8
45-54	12.5	7.7	9.6	13.2	7.7	9.6	11.6	7.7	9.6	11.6
54-64	11.4	5.0	6.6	13.2	6.3	8.2	13.4	6.3	8.2	13.4
65+	9.7	4.5	6.5	13.4	7.1	8.7	18.9	7.1	8.7	18.9
Risk of infection	5.5 ^a	—	—	—	3.7	1.8	0.5	3.7	1.8	0.5

— Not available.

Note: Based on age-specific mortality rates for each country and the estimated population age structure for the developing world in 1990.

a. 1938 figure.

Source: Authors.

consideration the age distribution of new cases and the relation between case-fatality rates and age. Clearly, the relation is complex; for example, the death rates may also vary by age because certain age groups or sexes may be more likely to seek treatment and be cured. For example, comparing the distribution of smear-positive patients by age and sex between Malawi and Tanzania, it is evident that women in Tanzania are much less likely to seek care than men. The reduction of female case-detection rates by sex bias in access to care is probably quite widespread, especially in South Asia. Tuberculosis case-fatality rates tend to increase steadily at older ages (Berg 1939; Styblo 1984). We have derived from the Berg data the relation between age-specific case-fatality rates with some data from Styblo (1984) on mortality in the age group zero through fourteen.⁴ Figure 11-5 provides the crude estimates of the age pattern of tuberculosis deaths in a country with an annual risk of infection of 1 to 2 percent, where the probability of detection is equal for smear-positive tuberculosis across all age groups and equal for other tuberculosis across all age groups.

This estimated pattern can be compared with the age distribution of tuberculosis deaths in Western countries when the annual risk of infection was similar to that now seen in the developing world. The age distribution of tuberculosis deaths adjusted to the age structure of the developing world in Czechoslovakia, Norway, and the Netherlands (Tuberculosis Surveillance Research Unit 1966) is illustrated in table 11-7. The percentage of deaths in children under fifteen ranged from approximately 10 to 20 percent. However, overall, the tuberculosis death rates in children were considerably lower in the Netherlands than in Czechoslovakia, even at higher risks of infection. Clearly, there are other variables that are significant determinants of the reported age distribution of tuberculosis death rates. One explanation may be the high rates of *M. bovis* infection in the Netherlands at the time. According to our estimates for Tanzania, 11 percent of tuberculosis deaths occur

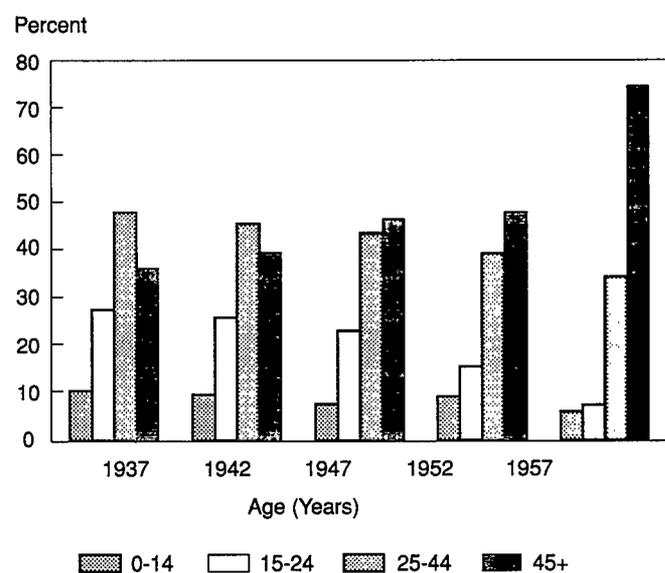
in children under age fifteen, which is within the lower range for the three industrial countries in table 11-7. The comparatively lower value may be a result of the higher BCG coverage in Tanzania now than in these countries at the time. Variation in the age pattern of tuberculosis deaths highlights the tentative nature of the estimates presented here. The basic conclusion, however, that tuberculosis is concentrated in the adult age groups, appears to be robust.

As implied in this discussion, the age pattern of tuberculosis deaths shifts toward higher ages as the annual risk of infection declines. Using data from the United States which has been adjusted to the 1990 age structure of the developing world, we demonstrate in figure 11-6 how the mean age of death increases as the risk of infection declines. The number of deaths in children declines faster than the annual risk of infection; this relationship will become important when we consider the cost-effectiveness of BCG.

Trends in Incidence and Mortality

We have estimated cases and rates of tuberculosis in the year 2015 using the midpoints of the ranges of the annual risk of infection in table 11-1, population projections, and the rates of decline in the annual risk of infection, also reported in table 11-1 (table 11-8). These estimates are based on the assumption that the rates of decline in the annual risk of infection observed between 1970 and 1985 will continue into the future. In other words, the projections are based on the assumption that the socioeconomic changes and tuberculosis control activities that caused the decline in the risk of infection in the last two decades will continue at the same rate. Such projections suffer

Figure 11-6. Shifting Age Structure of Tuberculosis Deaths in the United States, 1937



Note: Adjusted for age structure changes.

Source: Authors.

Table 11-8. Projected Cases and Deaths for all Forms of Tuberculosis in 2015

Area	Cases			Deaths
	Smear-positive	Other	Total	
Sub-Saharan Africa ^a	1,270,366	1,549,846	2,820,212	1,257,791
North Africa and western Asia	128,607	156,900	285,507	80,288
Asia	1,873,615	2,285,810	4,159,424	1,487,316
South America	98,667	120,373	219,040	67,965
Central America and the Caribbean	79,980	97,575	177,555	76,919
Total	3,451,235	4,210,504	7,661,738	2,970,279

Note: These projections are based on the following assumptions: (a) the current rate of decline in the annual risk of infection will continue over the next twenty-five years except in Sub-Saharan Africa, where it will not change because of the HIV epidemic; (b) the percentage of cases detected will remain the same in each region; (c) the percentage of patients treated with standard and short-course chemotherapy, and thus the population cure rate, will remain constant.

Source: Authors.

from all the same limitations as any projection of current trends. For Sub-Saharan Africa, we have assumed no net increase in the seroprevalence of HIV and no net decline in the annual risk of infection in making these projections to represent the potential contribution of the HIV epidemic. This is an extremely conservative assumption that probably underestimates the contribution of HIV-associated tuberculosis to the total tuberculosis caseload and the real potential for an increase in the risk of infection in the HIV-negative population, given an increasing number of sputum-positive patients. According to these conservative assumptions, tuberculosis will remain a significant problem in all developing world regions referred to in table 11-8. In Africa, population growth alone will lead to an absolute increase in the number of cases.

Social and Economic Costs

There are few if any studies of the actual costs or consequences of tuberculosis on the family, community, or economy in developing countries. The special burden of ill health and death caused by tuberculosis, however, follows from the age distribution of its incidence. Although morbidity and mortality in any age group have significant social and economic costs, the death of adults in their prime, who are the parents, community leaders, and producers in most societies, cause a particularly onerous burden. The incidence of tuberculosis is concentrated in adults age fifteen through fifty-four. For example, whereas the overall incidence in Africa of tuberculosis in 1985 is estimated to be 260, in adults it is approximately 390 per 100,000.

One of the greatest costs to society and the economy from tuberculosis is mortality. It has been estimated that there are just under 10.6 million deaths in adults age fifteen through fifty-nine in the developing world (Murray and Feachem 1990). Of these, our figures suggest that approximately 18.5 percent are due to tuberculosis. Not all these deaths are preventable.

Of avoidable adult deaths, 26 percent are probably due to tuberculosis.

The consequences of adult death from tuberculosis on children and other dependents can also be great. Studies have shown that, when a mother dies, her children suffer higher rates of mortality (Greenwood and others 1987). One can speculate that similar relationships exist for paternal death. Several studies from industrial countries have shown that tuberculosis is concentrated in lower socioeconomic groups, those households least able to cope with the burden of tuberculosis. Pryer (1989) found that in households in which one parent suffers from a serious debilitating disease, such as tuberculosis, children are two and one-half times more likely to be severely malnourished. Because tuberculosis deaths are concentrated in the segment of the population that is economically most productive, the economic cost of tuberculosis in lost production must be greater than that of a disease that exclusively affects children or the elderly.

Prevention

Before discussing specific measures to prevent or treat tuberculosis in developing countries, we will summarize the rationale for tuberculosis control programs in countries with a low prevalence of HIV infection. The presence of a significant proportion of the population infected with HIV may change the strategy for control.

- Unlike many other infectious diseases seen in developing countries, tuberculosis can be controlled with existing tools because the infectious agent is almost exclusively in the diseased person, who can be quickly rendered noninfectious.
- The detection of infectious, particularly smear-positive, cases of pulmonary tuberculosis and their cure are the key to effective prevention and control of the disease, both in industrial and developing countries. In addition, detection and treatment of cases reduce suffering and if adequately applied, very much lower the death rate of tuberculosis.
- Because a balance exists in developing countries between the tubercle bacillus and people in the absence of human-made interference (that is, case finding and chemotherapy), any reduction in the sources of infection will inevitably improve the epidemiological situation. If all or nearly all smear-positive cases of pulmonary tuberculosis diagnosed at present in any developing country could be rendered noninfectious, the risk of tuberculous infection would immediately start to fall. A decrease in the annual risk of tuberculous infection of 4 percent or more would not only result in a decrease in the incidence rate of the disease but would also outweigh increases in the population; consequently the absolute number of smear-positive cases would fall as well. A 5 percent decrease in the risk of infection each year would ensure that the tuberculosis problem in a given community or country would halve itself about every fourteen years.

- Reliable diagnostic tools that enable detection of the great majority of smear-positive cases of pulmonary tuberculosis and highly efficient chemotherapy regimens that can cure nearly all discovered cases of tuberculosis are available.

There are three main strategies for preventing tuberculosis: BCG vaccination, chemoprophylaxis, and decreasing sources of infection through case treatment. Each will be discussed in turn.

BCG Vaccine

The bacillus of Calmette and Guérin (BCG) was developed in 1921. Since that time it has become one of the most widely used yet controversial vaccines. Although BCG coverage has been up to now quite high on average compared with other immunizations, the effectiveness of BCG in preventing tuberculosis in adults remains controversial. From clinical trials conducted in the United Kingdom and in the United States it was found that BCG was up to 80 percent effective (Aronson, Aronson, and Taylor 1958; Great Britain Medical Research Council 1972). Important vaccine trials in southern India, however, revealed no effectiveness of BCG (Tuberculosis Prevention Trial 1979; Tuberculosis Prevention Trial, Madras 1980). Reports from a variety of prospective trials in the industrial world and more recent case-control studies in developing countries state effectiveness ranging from 0 to 80 percent (Clemens, Chung, and Feinstein 1983; Smith 1987).

Many explanations and theories have been advanced to explain this variance, including differences in strains of BCG, infections with other mycobacteria, and differences in susceptibility resulting from factors such as nutritional status (Fine 1989). Although there is no consensus on the effectiveness of BCG, we will assume that BCG is between 40 and 70 percent effective in preventing tuberculosis in children age zero through fourteen when given at birth. Some would argue that BCG given at birth may protect beyond fifteen years; there is, however, no evidence of this, especially in developing countries.

The BCG vaccine is given as early as possible in life, preferably at birth, in the vast majority of developing countries. Serious consideration might also be given to "indiscriminate (re)vaccination" (that is, without prior tuberculin testing) at older ages, irrespective of vaccination at birth. Depending on the feasibility of coverage, BCG (re)vaccination could be given to children entering and leaving school, pregnant women during prenatal care visits to health facilities, or to the general population during routine contacts with health workers. For example, tetanus toxoid is now considered by many to be an integral component of prenatal care; BCG could be delivered at the same time for only a small increase in the total cost. The actual effect of BCG (re)vaccination at older ages has not been studied; there seems little reason to believe that it would be harmful, however, and it may have some beneficial effect.

Still, we must realize that vaccination of newborns with BCG is a problem in those developing countries where there is a high

prevalence of HIV infection among mothers. The WHO Expanded Programme on Immunization, which is responsible for the program of vaccination against six selected childhood diseases in the world, has been continuing BCG vaccination of newborns and small children, including those whose mother is known to be or suspected of being infected with HIV. As of the time of writing, evidence remains inconclusive regarding the rate of adverse reactions after BCG immunization among asymptomatic HIV-infected individuals. The vaccine should be withheld from individuals with symptomatic HIV infection (WHO 1987).

The effect of mass BCG vaccination on the epidemiological situation of tuberculosis was overestimated until the mid-1970s (Styblo and Meijer 1976). As mentioned earlier, tuberculosis is largely transmitted by persons with sputum smear-positive pulmonary tuberculosis. From the age distribution of smear-positive patients, it is clear that even complete BCG coverage can have little effect on the annual risk of infection. Total coverage with BCG, however, will have a significant effect on tuberculosis mortality in children, if BCG is 40 to 70 percent effective, as we have assumed. Based on the assumptions discussed above, complete coverage could reduce total tuberculosis mortality by 4 to 7 percent. The vaccine will most likely have very limited effect on the remaining 90 percent and more of tuberculosis mortality. Evidently, the expansion of BCG coverage alone cannot or should not be the sole means employed to control tuberculosis in any community.

Cost-Effectiveness of BCG

For two principal reasons, generalizable estimates of the cost-effectiveness of BCG cannot be made. First, there may be substantial differences in the computed average and marginal costs of BCG programs, depending on the program considered. Second, the cost-effectiveness of BCG is inversely proportional to the annual risk of infection.

When more than one vaccine is given at the same time, average costs for delivering each particular immunization are often calculated by dividing the cost per client contact by the number of vaccinations received. Thus the difference between marginal costs and average costs for a BCG program will depend on whether BCG is delivered in an independent campaign, in a contact with mother and child, or along with other immunizations such as the first DPT (diphtheria-pertussis-tetanus) vaccination. The Expanded Programme on Immunization has not, unfortunately, collected data on how BCG is delivered in each country. We conclude that the marginal cost-effectiveness of expanding BCG will necessarily depend on the location and timing of vaccination in a particular country.

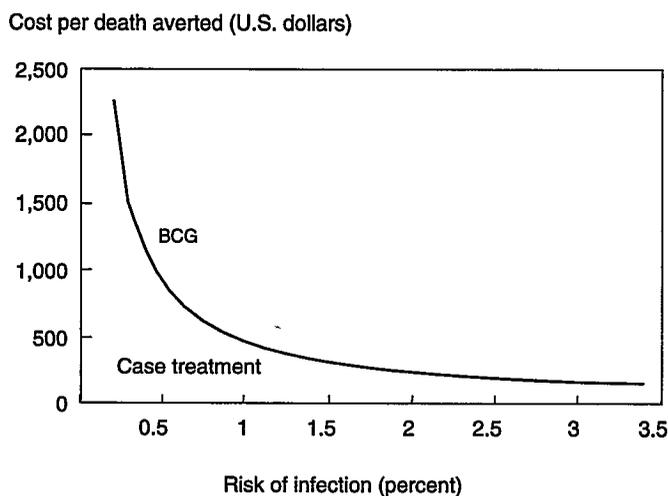
As the annual risk of infection declines, if all else remains the same, the cost of immunizing all newborns does not change. The benefits of BCG immunization in cases or deaths averted, however, will decline inversely to the risk of infection. For example, as the risk of infection declines from 2 percent to 1 percent, the cost per death averted will more than double. The increase in the cost per death averted is greater than the

decline in the risk of infection because the age distribution of deaths also shifts away from children as the risk of infection declines (see figure 11-6). The expected relation between the risk of infection and the cost per death averted by BCG is illustrated in figure 11-7.

In only one study has an attempt been made to cost a BCG program and estimate its effect in a developing country. Barnum, Tarantola, and Setaidy (1980) estimated the cost of operating a BCG program alone and also the marginal cost of adding a BCG program to an existing DPT program. Their estimates of deaths averted were based on local incidence and case-fatality rates of tuberculosis and an assumed effectiveness for BCG of 50 percent. Using their original data, we have recalculated the cost per discounted death averted in U.S. dollars.⁵ Deaths prevented by BCG vaccination now occur over the next fourteen years; these are discounted to present value for comparison with interventions that avert deaths in the current time period. The cost in 1986 U.S. dollars per death discounted at 3 per cent was \$644 for the BCG program alone and \$144 for the marginal BCG program. At the time in Indonesia, survey data suggested that the risk of infection was approximately 3 percent: regional surveys reported annual risks of infection of between 2 and 4 percent (Cauthen, Pio, and ten Dam 1988). It must be stressed that these estimates of cost-effectiveness do not take into consideration the potential benefits of BCG in reducing leprosy (Fine 1989).

With no evidence at all on the efficacy of indiscriminate adult (re)vaccination with BCG, it is difficult to discuss the cost-effectiveness of adult BCG vaccination. Because tuberculosis mortality is concentrated in the young adult ages, revaccination, if it proved to be as effective as the vaccination of infants, would be more cost-effective. This, of course, assumes

Figure 11-7. Cost-Effectiveness of BCG and Case Treatment as a Function of the Annual Risk of Infection



Source: Authors.

that delivery of BCG to adults could be feasible at the same average or marginal costs as its delivery to infants.

Chemoprophylaxis

Secondary prevention of clinical tuberculosis can be accomplished by treating patients with tuberculosis infections. Chemoprophylaxis is applied either to freshly infected so-called tuberculin converters or to those who have been infected with virulent tubercle bacilli in the more distant past. The latter either do or do not have abnormalities in the lungs on x-ray.

Tuberculin converters undoubtedly represent a very rewarding group in terms of chemoprophylaxis results and thus chemoprophylaxis policy has been adopted as a routine procedure in a number of low-prevalence countries. Mass chemoprophylaxis of converters is impossible, however, since their identification depends on repeated tuberculin tests of the population. However, a selective search for converters in high-risk groups, such as close family contacts of smear-positive sources, is a feasible alternative. As discussed later, 6 to 10 percent of recent infections evolve into clinical tuberculosis. In developing countries, where large percentages of the population have been infected, the International Union against Tuberculosis and Lung Disease (IUATLD) recommends chemoprophylaxis only for all non-BCG-vaccinated children age five years or under, with no symptoms of tuberculosis. In children with symptoms, standard treatment should, of course, be given.

Chemoprophylaxis in tuberculin-positive subjects who have not developed clinical tuberculosis would reduce the number of sources of infection, if given for six to twelve months. In most developing countries, this group is very large, and resources would be far better directed to the detection of cases and to treatment. Still, chemoprophylaxis might play a very important role both in industrial and developing countries in subjects with the dual HIV and tuberculous infections but without clinical and bacteriological signs of tuberculosis. Research on HIV chemoprophylaxis is under way in several Sub-Saharan African countries.

Studies in industrial countries have found cost-effectiveness ratios per case averted to be greater than \$7,000 for a twenty-four-week regimen (Snider, Caras, and Koplan 1986). Without accurate data to review the cost-effectiveness of chemoprophylaxis in developing countries, we can only make some comparisons with the costs per case treated. Because only 6 to 10 percent of those who have recently become skin-test positive develop clinical diseases, 10 to 16.7 recent tuberculin-positive patients must be given chemoprophylaxis to prevent one case of tuberculosis, assuming prophylaxis is 100 percent effective. In tuberculin-positive patients as opposed to new converters, the ratio would be one or two orders of magnitude higher because the long-term breakdown rate is only 25 to 40 per 100,000 per year. The drug costs for chemoprophylaxis are lower than for treatment, but the costs of administration, screening, transport, delivery, and monitoring would be similar. Thus, chemoprophylaxis is unlikely to be more cost-effective in developing countries than case treatment of

patients presenting with symptoms suggestive of tuberculosis as discussed later. One exception may be in children under five exposed to an adult with active smear-positive pulmonary tuberculosis.

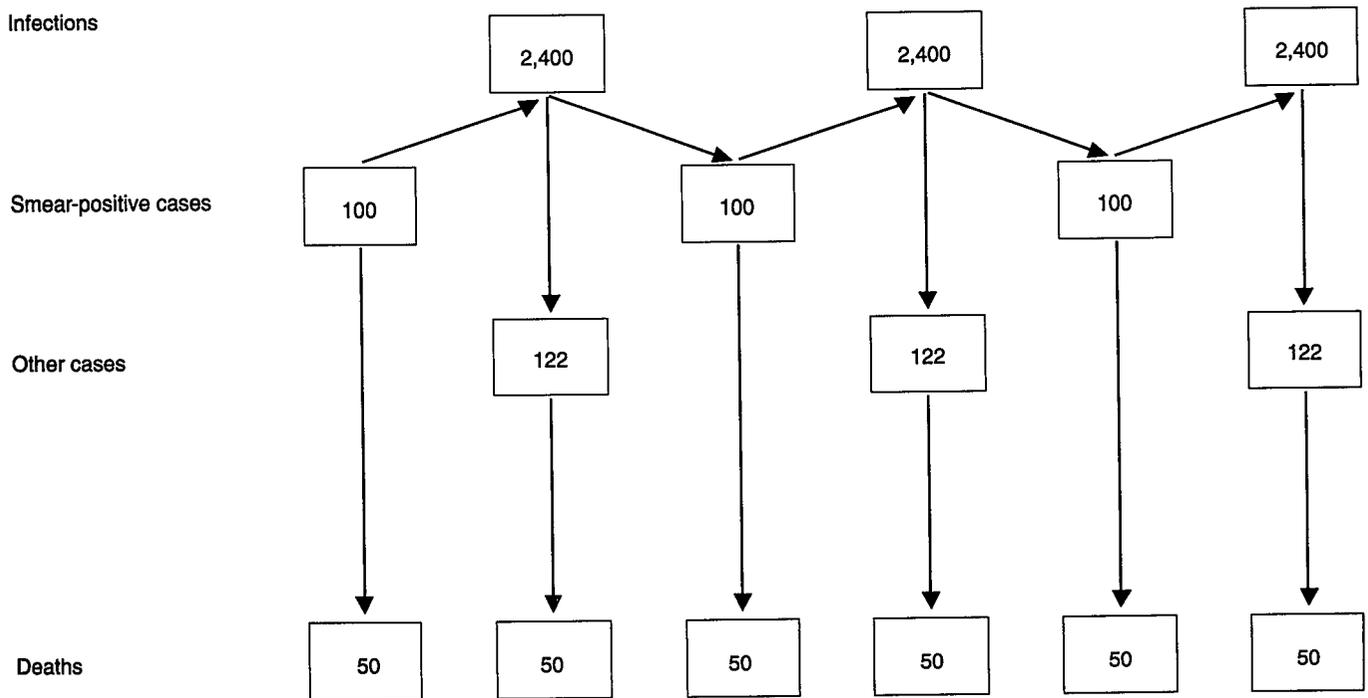
Decreasing Sources of Infection

The transmission of tuberculosis appears to take an extremely regular and stable course in comparison with most other infectious diseases such as malaria, schistosomiasis, or cholera. Each infectious or smear-positive person infects many others each year. The number of new infections caused each year by a person with smear-positive tuberculosis can be estimated from survey data on the number of new infections and the prevalence of smear-positive tuberculosis. It has been estimated from data from developing and industrial countries that an undiagnosed and untreated smear-positive source of tuberculous infection would infect on average between ten and fourteen persons per year (Sutherland and Fayers 1975; Styblo 1984). Each smear-positive person continues to excrete the bacillus for an average of two years, thus leading to the well-known 2:1 ratio of prevalence to incidence (Styblo 1984). A person with smear-positive tuberculosis will be responsible for approximately twenty to twenty-eight new infections before either dying or becoming smear negative. Figure 11-8 is an illustration in a schematic form of the nature of tuberculosis transmission.

A certain percentage of these new infections or reinfections caused by a smear-positive person will in turn break down and lead to clinical tuberculosis. Reference is made to three reports of newly infected persons to determine the percentage that developed clinical tuberculosis: the British Medical Research Council study (Sutherland 1976) found that 8.1 percent of converters developed clinical tuberculosis within fifteen years; in Saskatchewan, 6.4 percent of recently infected individuals developed clinical tuberculosis within a few years after primary infection (Barnett, Grzybowski, and Styblo 1971); and a Tuberculosis Surveillance Research Unit study of European data found that 6.0 percent of converters developed bacillary tuberculosis in five years (Sutherland 1968)). For the purposes of modeling transmission, we will assume that from 6 to 10 percent of new infections will eventually develop some form of clinical tuberculosis.⁶ In figure 11-8 we show that the new infections could lead to 100 cases of smear-positive tuberculosis and 122 cases of smear-negative or extrapulmonary tuberculosis. The transmission cycle would then repeat itself over and over.

The steady state illustrated in figure 11-8 is a close approximation of reality in most of the developing world. Data on the annual risk of infection summarized in table 11-1 showed that the annual decline in the risk of infection for Africa and Asia was between 1 and 3 percent. Population in these regions is also growing at an annual rate of 1 to 3 percent, so the absolute number of cases of smear-positive tuberculosis remains nearly

Figure 11-8. Tuberculosis Transmission Schematic



Source: Authors.

constant. In other words, each smear-positive case of tuberculosis must lead on to approximately one more smear-positive case after a round of transmission. The best way to prevent tuberculosis, therefore, is to interrupt the transmission cycle. As early as 1961, Crofton (1962), realized that chemotherapy for smear-positive patients, which rapidly renders them non-infectious, is the best way to reduce the transmission of the disease.

Risk Factors

The history of tuberculosis in industrial countries clearly demonstrates an important role for socioeconomic change in the decline of tuberculosis. In figure 11-9 we show how the age-specific tuberculosis mortality rates in the United States declined from 1900 to 1950, before chemotherapy was available. This decline appears to have been due to a decrease in transmission, because the case-fatality rates remained constant in this period (Drolet 1938). Reduction in transmission may have been a result of improvements in housing, nutritional standards, general health, and perhaps most important the policy, instituted at the turn of the century, of isolating infectious sources of tuberculosis in sanatoriums. During the first four decades of this century the annual risk of infection in most industrial countries was falling about 3 to 5 percent per year (Styblo 1984).

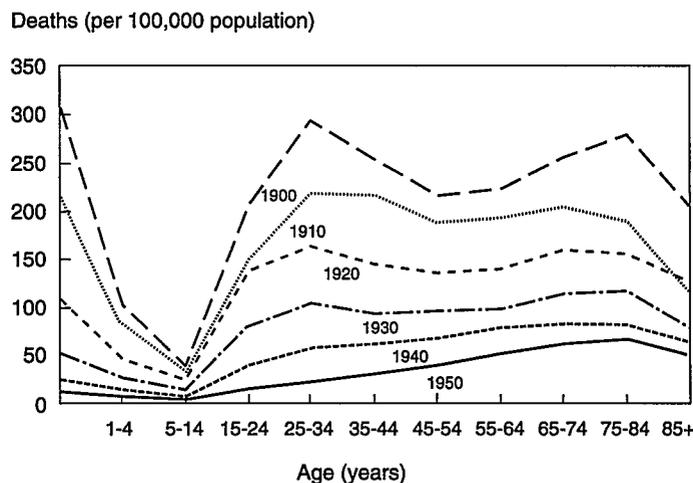
With the introduction of chemotherapy, tuberculosis mortality rates declined at a faster rate, approaching 10 to 12 percent. In some developing countries that have reliable registration of vital statistics, such as Chile, tuberculosis mortality was fluctuating and high before 1945, after which it declined precipitously. The most famous example of the effect of chemotherapy is in the Eskimos. In populations in Canada and Greenland, the risk of infection before 1950 approximated 25 percent per year. After aggressive case detection and treatment were instituted, the annual risk of infection declined by 17 to 20 percent per year. Tuberculosis mortality has followed a similar precipitous decline (Johnson 1973; Grzybowski, Styblo, and Dorken 1976).

The experience of industrial countries, and some disadvantaged groups in these countries, indicates that although socioeconomic changes can reduce the transmission of tuberculosis, widespread use of chemotherapy can greatly accelerate the decline in tuberculosis. In many parts of the developing world tuberculosis is declining at a rate of 1 to 2 percent per year. Improved case detection and case treatment could realistically accelerate that decline to 5 to 10 percent per year.

Three specific risk factors for developing tuberculosis deserve note. First, for the last few years we have been witnessing the strongest risk factor for developing tuberculosis in individuals remotely or recently infected with tubercle bacilli-HIV infection. The mechanism is easy to understand: the decrease in immunity caused by HIV infection results in the flaring up of this virulent agent, the tubercle bacillus.

Tuberculosis is thus one of the diseases in developing countries most influenced by the HIV pandemic. The interactions

Figure 11-9. Age-Specific Tuberculosis Death Rates in the United States, 1900-50



Source: Vital and Health Statistics

between HIV and tuberculosis infections, particularly in countries where both infections are prevalent, appear more and more clearly. In several African countries, a considerable increase in newly discovered cases has already been documented (for example, Tanzania and Malawi). Tuberculosis is a frequent presenting symptom of HIV infection and AIDS in these and other countries.

The WHO Global Programme on AIDS, the WHO tuberculosis unit, and the IUATLD have initiated studies on the study on the various facets of the interactions of these two diseases, particularly, the epidemiological effect of HIV infection on the overall tuberculosis situation. Researchers suspect not only that HIV infection will increase the incidence of tuberculosis in individuals already carrying the tubercle bacillus, as a result of the decrease in immunity, but that the excess sources of infection will result in an increase in the annual risk of tuberculosis infection in the country.

The two other specific potential risk factors for developing tuberculosis are mining and associated silicosis and malnutrition. The association between silicosis and tuberculosis has long been noted (Brink, Grzybowski, and Lane 1960). This relationship may explain in part the high incidence of tuberculosis in southern Africa and the Altiplano of South America, where a significant proportion of the adult male population works in mining and where there is an elevated prevalence of silicosis (De Beer 1984). Although the validity of this hypothesis has not been rigorously tested, the association between silicosis and high incidence of tuberculosis is accepted by many authors.

Malnutrition has been associated with increased incidence of and deaths from tuberculosis. During World War II, tuberculosis rates increased in European countries affected by the war, particularly in some special groups, such as in camps (Cochrane 1948) and in the Warsaw Ghetto

(Schechter 1953). There has been, however, no careful, controlled demonstration of this association, because crowding, recirculating air, and poor sanitation seem to be at least as important. Conversely, despite improvements in nutritional intake, the case-fatality rate for tuberculosis remained unchanged in the United States, England, Denmark, and other industrial countries from the turn of the century until the introduction of chemotherapy. Improvement in nutritional status may alter the probability of those who are infected developing clinical tuberculosis, and it may decrease the breakdown rate from infection to disease. As a pragmatic means of preventing tuberculosis, however, improving the general nutritional status of the population holds little promise, unless it is combined with an efficient program of case detection and treatment.

Curative Care

The subject of curative care can naturally be divided into tuberculosis detection and chemotherapy. We will address each of these in turn, highlighting the policy options.

Case Detection

There are two main issues in detecting cases of clinically significant tuberculosis: active as opposed to passive detection strategies and the choice of diagnostic technology. "Active detection" means an attempt to screen the population at large or target populations, such as military recruits, for evidence of tuberculosis. "Passive detection" means screening and diagnosing only those patients who visit a health service provider because of symptoms suggestive of tuberculosis. In the 1950s and 1960s, the choice between active and passive detection in industrial and developing countries was a controversial topic (Styblo and others 1969; Meijer and others 1971; WHO 1974; Toman 1979; Styblo and Meijer 1980). In the last two decades, a consensus for passive case detection of tuberculosis in all countries has developed—both WHO and the IUATLD advocate this policy.

Three assumptions underlie the wide acceptance of passive case detection as the primary strategy in tuberculosis control. First, 90 percent of patients with smear-positive pulmonary tuberculosis have objective symptoms, such as cough, fever, loss of weight, sputum, or hemoptysis. These symptoms develop quite soon after the onset of the disease, prompting the patient to seek medical advice. Second, the great majority of sputum smear-positive tuberculosis cases develop in a shorter period of time than the shortest feasible interval between two mass radiography survey rounds. That is why smear-positive tuberculosis cases were detected outside (and usually earlier than) the periodic case-finding campaigns conducted by the regular health services. Third, appropriate diagnostic and curative care ought to be physically, socially, and economically available. Most infections, before chemotherapy is instituted, would therefore occur within the family. Whereas in industrial countries it is estimated that two to three persons would be

infected by a person with smear-positive tuberculosis before its detection, this number may be four or five in developing countries, because of a higher number of close contacts. No contacts will be infected after the start of adequate chemotherapy. The validity of these assumptions depends on local conditions, cultural perception of disease, access to care, and the effectiveness of health services.

Regardless of the technology used, active case detection is more expensive per case detected because the yield of tuberculosis per patient screened is lower. For example, if the incidence of smear-positive tuberculosis is 100 per 100,000 people, then the sputum of more than 1,000 people would have to be screened to detect one case of smear-positive tuberculosis, provided it is the general population that is being screened. If specific high-risk groups were identified, the yield would clearly be higher. For comparison, the use of sputum microscopy to screen patients who present with cough in Tanzania yields one patient in ten with smear-positive tuberculosis. Another argument against active case detection is that persons actively identified as being infected may be less likely to comply with long drug regimens. Clearly, they did not yet consider their health to be impaired enough to seek treatment. Moreover, a proportion of smear-negative persons with few or no clinical symptoms cure spontaneously and in a number of cases the disease is in regression (Styblo and others, 1969; Meijer and others 1971; National Tuberculosis Institute, Bangalore 1974). In developing countries, active case finding was studied by the Kenyan and British Research Councils in the late 1970s and early 1980s. These studies have yielded seven reports, and the conclusion in the last study is that a patient suffering from symptoms suggestive of pulmonary tuberculosis nearly always seeks medical advice from a health unit, usually several times. In many instances, however, health workers at the peripheral level do not think of tuberculosis and do not examine the sputum themselves or do not refer the patient to the nearest microscopy center for sputum examination for tubercle bacilli. In many developing countries, public transportation is rudimentary; even if available, it is not always affordable to poor people. Moreover, the Kenyan studies have shown that active case finding, except in health units, is not feasible.

The second issue in case detection is the choice of technology. At present, the main options are sputum microscopy, sputum culture, and radiology. To illustrate the yield and likely cost of case detection using microscopy (Ziehl-Nielsen stain), we shall examine data from the National Tuberculosis and Leprosy Programme in Tanzania. In that country, one in seven people who are suspected of having tuberculosis and are screened is identified as having smear-positive tuberculosis. Normally, three smears are conducted on each patient. The cost of supplies and reagents alone for these thirty smears is \$2.50. A microscopist can examine about twenty sputa per day. The effective cost per case detected using sputum microscopy in Tanzania is \$5.46, including the depreciated cost of the microscopes. In Tanzania, three sputa are examined to increase test sensitivity; the increased sensitivity achieved with the

third smear is in fact small and could be sacrificed to reduce the cost.

Sputum culture is used to diagnose pulmonary tuberculosis in those patients who produce too few bacilli to be detected on a smear, to confirm sputum microscopy, and to characterize the type of mycobacterium. Because culture takes several weeks to yield results, it is not useful as a primary diagnostic tool in developing countries. For retreatment cases, however, culture and sensitivity may be very important to determine the most cost-effective drug regimen.

There are at least two different roles for chest radiography in the diagnosis and treatment of tuberculosis. First, for diagnosing smear-positive tuberculosis, chest radiography can be used to identify a group with a much higher probability of being smear positive. The resulting yield on sputum microscopy can be increased and many fewer total smear examinations undertaken. In areas where the prevalence of smear-positive tuberculosis is low, the increased yield may be important for maintaining the quality of sputum examinations. Unfortunately, x-rays are not 100 percent sensitive in detecting tuberculosis, so an initial screening with chest radiography will decrease the total yield as compared with sputum culture—for example, in Bangalore, x-ray was 87 percent sensitive. Second, chest radiography is essentially the only available tool for use in the periphery of most developing countries for the diagnosis of smear-negative tuberculosis. Sputum culture, although the gold standard for smear-negative diagnosis, takes too long and is too difficult to implement in the periphery of most developing countries. The role of chest radiography depends on the desirability of detecting and treating smear-negative tuberculosis; this subject will be discussed later in relation to cost effectiveness.

The cost per case of tuberculosis detected by x-ray depends largely on three factors. First is the prevalence among symptomatic patients presenting with x-rays suggestive of tuberculosis at health services. This can reportedly vary from one in two in China to a more realistic rate of one in four or five in Tanzania. The second factor is the cost of x-ray machines, which are expensive capital investments. The depreciated capital cost per patient screened depends on how much the machine is used. A district-level machine used for the diagnosis of many diseases is likely to be less expensive per patient than an underused machine dedicated to the detection of tuberculosis. Considerations of depreciated capital cost will require x-rays to be used at a level in the health services that has an adequate patient load. On the basis of hypothetical cost calculations, the cost per case of tuberculosis detected using chest radiography varies from \$6 to \$10 in China and Tanzania, assuming a caseload of 5,000 x-rays per year on a machine that costs \$50,000 and lasts ten years. More research is needed on defining the true average and marginal costs of deploying chest radiography in various conditions for the diagnosis of smear-negative pulmonary tuberculosis.

New diagnostic technologies based on the enzyme-linked immunoabsorbent assay or DNA probes for mycobacterial DNA or RNA are currently being investigated (Daniel 1989; Bloom

1989). If these technologies yield new tools that can be inexpensively applied in developing countries, passive case detection may be improved, especially for smear-negative and extrapulmonary tuberculosis, which cannot be diagnosed by sputum microscopy. Active case detection in some high-risk groups would perhaps become feasible.

A limited number of interventions are available to improve the effectiveness of passive case detection. The factors that would be most important in improving such effectiveness are a high cure rate of diagnosed cases and a friendly relationship between the treating health staff and the patient. Public education can increase general awareness of the symptoms of tuberculosis and encourage those suspected of having it to seek medical advice. Improved diagnostic skills of primary health care providers, transport of sputum or a patient to a microscopy center, and availability of x-ray facilities can also improve the detection of both smear-positive tuberculosis and other tuberculosis. Finally, if diagnosis and adequate treatment are free, as recommended by WHO and IUATLD, more patients will seek early care.

Treatment

The first antituberculosis drug, streptomycin, became available in the early 1940s. In 1952, three antituberculosis drugs were available (streptomycin; para-aminosalicylic acid, or PAS; and isoniazid) which were able to cure virtually all patients however severe their disease, provided that their bacilli were initially sensitive to the above drugs. Such results were achieved in Edinburgh in 569 cases as far back as 1953 and 1954 and in 2,506 cases treated in 1955–56 (Crofton 1961). Since then a variety of chemotherapeutic agents have been developed. The six drugs recommended by WHO and the IUATLD and most commonly used in developing countries for tuberculosis are isoniazid, streptomycin, thiacetazone, ethambutol, rifampicin, and pyrazinamide. These drugs are used in a host of combinations for different durations (table 11-9).

Despite the availability of powerful and potentially effective antituberculosis drugs, tuberculosis treatment programs in most developing countries have not been very successful. Overall cure rates for most national programs in poor developing countries are below 50 percent. Evidently, the “standard” chemotherapy (isoniazid, streptomycin, and thiacetazone) recommended by the WHO Expert Committee on Tuberculosis (WHO 1974) for use in developing countries is presently, and probably will be in the future, beyond the organizational resources of many of them. This was clear to Canetti more than thirty years ago. As the principal reporter to the Panel on Eradication of Tuberculosis he stated: “On the global level, and among the efforts required to make some headway towards tuberculosis eradication, an absolute priority stands out imperatively: to develop chemotherapeutic methods adapted to the conditions prevailing in underdeveloped countries” (Canetti 1962).

In the 1960s and 1970s, experience showed that Canetti was right. In many poor developing countries in Africa, many parts

Table 11-9. Examples of Anti-tuberculosis Chemotherapy Regimens Used in Developing Countries

Regimen	Duration (months)
<i>New smear-positive standard</i>	
2SH/10TH	12
2SH/10EH	12
2SH/10S ₂ H ₂	12
<i>Short-course</i>	
2SHRZ/6TH	8
2SHRZ/4HR or 2EHRZ/4HR	6
2HRZ/4HR	6
2RZ/4H ₃ R ₃	6
<i>New smear-negative</i>	
2STH/10TH	12
2SHRZ/6TH	8
<i>Retreatment</i>	
2SHRZE/1HRZE/5H ₃ R ₃ E ₃	6
2SHRZE/1HRZE/5TH	8

Note: S = streptomycin 1 gm; H = isoniazid 300 mg; R = rifampicin 450/600 mg; Z = pyrazinamide 1500/200 mg; E = ethambutol 25 mg/kg; T = thiacetazone 150 mg. Subscripts indicate the number of times each week drugs are given during intermittent therapy.

Source: Authors.

of Southeast Asia, and certain parts of Latin America, signs of improvement in the epidemiological situation of tuberculosis were the exception, despite widespread attempts at disease control. The most important reason for the failure of such control programs was the low cure rate. As Canetti postulated, unless a large increase in the cure rate for smear-positive pulmonary tuberculosis can be achieved, there will be no marked improvement in the tuberculosis problem in many developing countries in the foreseeable future.

Although there are many interesting issues in tuberculosis treatment, in this discussion we will stress the choice between WHO standard chemotherapy regimens that last from twelve to eighteen months and use fewer and cheaper drugs (isoniazid, streptomycin, and thiacetazone), and short-course chemotherapy that lasts from six to eight months and uses multiple and more expensive drugs (rifampicin and pyrazinamide). To compare these two strategies with chemotherapy, we must examine the relative effectiveness of each and the relative costs of each. Because of the great diversity in effectiveness and costs between countries, the emphasis will be on the key determinants of the effectiveness and costs of the two regimens. It should be stressed that the regimen with a higher cure rate leads to a more rapid reduction in the risk of tuberculosis infection and the incidence of active tuberculosis.

Effectiveness of Chemotherapy

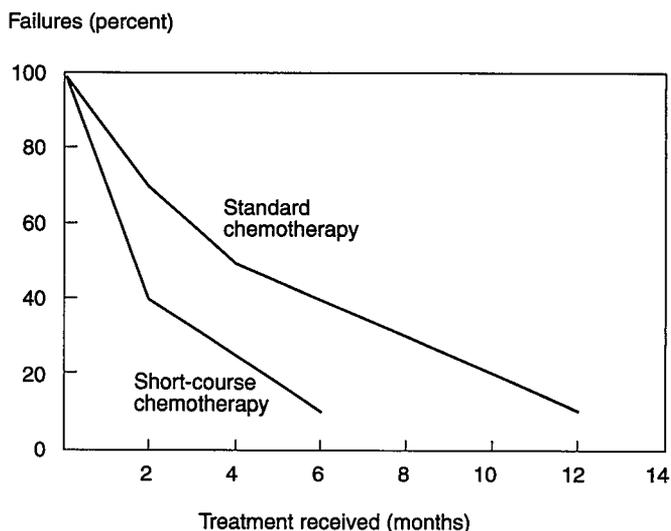
The effectiveness of standard and short-course chemotherapy depends on three main factors: the cure rate, acquired drug resistance, and the effect on the trend of the risk of tuberculous infection. Without question, the most important of these

factors today in nearly all contexts is the cure rate, which decisively influences the remaining two factors.

One determinant of the cure rate is the biological effectiveness of WHO standard and short-course chemotherapy given under ideal conditions of 100 percent compliance. With short-course chemotherapy, after two months of treatment 80 to 90 percent of smear-positive pulmonary cases will have converted to sputum-negative status. Under WHO standard therapy, after two months 50 percent will remain smear positive. The "permanent" cure rate is a more important aspect of the treatment regimens. In figure 11-10 we show the percentage of patients who will remain or become smear positive, say, two years after the start of the (first) treatment (with no retreatment during the first two years), provided that chemotherapy is discontinued at each point in time. We shall refer to them as "failures." (Patients who remained or became smear positive and died during the first two years will also be referred to as failures. Under short-course chemotherapy (for example, 2SHRZ/6TH [see table 11-9]), about 40 percent of those who discontinue chemotherapy at two months may be failures compared with approximately 10 percent of those who complete six months of short-course chemotherapy. Under standard chemotherapy (for example, 2STH/10TH), the failure rate in patients who discontinue standard chemotherapy after two months may reach 65 to 70 percent, and in those who complete six months it might be approximately 50 percent. The failure rate begins to drop significantly on WHO standard chemotherapy only after six months. By twelve months, under ideal conditions of 100 percent compliance, approximately 10 percent will become failures if treatment is stopped.

Since standard and short-course chemotherapy both give high cure rates and do not lead to secondary resistance in

Figure 11-10. Patients Failing Therapy after Two Years of Follow-up, as a Function of Months of Chemotherapy



Source: Author.

controlled clinical trials, compliance is the most important determinant of the cure rate in national tuberculosis programs. There is a vast and detailed literature on compliance in general and on tuberculosis in particular (WHO Tuberculosis Chemotherapy Centre 1963; Haynes, Taylor, and Sackett 1979; Fox 1983a, 1983b; Chauler 1987; Reichman 1987). Many of the factors that one might expect would influence patients' compliance with antituberculosis drug regimens, such as the severity of side effects, have not been empirically observed. There is a clear consensus, however, that the duration of treatment adversely affects compliance (Haynes 1979). Moodie (1967) in unusual circumstances in Hong Kong found that most noncompliers dropped out in the first three weeks; but all other studies have observed a steady dropping out over time (East African and British Medical Research Council 1977, 1979). Improved net compliance in shorter regimens is an important advantage of short-course chemotherapy over standard chemotherapy. Given the relapse rate as a function of months of treatment discussed above, in a situation where patients continue to drop out over time, short-course chemotherapy will have a higher total cure rate.

Another determinant of tuberculosis chemotherapy compliance is the degree of supervision of treatment. A spectrum exists, from giving supplies of drugs for multiple months to patients all the way to hospitalization for the entire duration of treatment. Between these extremes, a wide variety of supervision strategies are possible, including daily patient visits to health centers, health visitors contacting patients in the home, periodic urine tests to monitor compliance, and hospitalization for the first two months of treatment. Although increased supervision increases compliance in most settings (Haynes 1979), increased supervision also means increased cost. The balance of this tradeoff will depend on the specific institutional and cultural characteristics of each community. For example, in Madras, in areas where most of the population has ready access to health centers, entirely ambulatory care has been successful (Tuberculosis Chemotherapy Centre, Madras 1959; Dawson and others 1966). On the other hand, in many parts of rural Sub-Saharan Africa, the only way to guarantee daily supervision of chemotherapy may be to hospitalize patients for the first two months of chemotherapy; this has been the experience in seven African countries (Tanzania, Kenya, Mozambique, Malawi, Benin, Senegal, and Mali) (Styblo and Chum 1987).

The rationale for hospitalizing patients to ensure close supervision of the initial intensive phase is much greater in short-course chemotherapy than in WHO standard chemotherapy. Two months of short-course chemotherapy will convert smear-positive sputum into smear-negative sputum in about 90 percent of patients, and in another two to four weeks, in the remaining 10 percent. Even if they stop taking drugs one or two months after they leave the hospital, many will not relapse. In Tanzania, approximately 50 percent of smear-positive patients enrolled in WHO standard chemotherapy remain smear and culture positive at two months. For standard chemotherapy, it is crucial to continue to take isoniazid and thiacetazone

combined tablets daily for at least another two months to achieve 90 percent sputum conversion.

In all probability, the patient's perception of the effectiveness of treatment and the balance between discounted future costs and benefits of treatment are also important determinants of compliance. In Tanzania and other IUATLD-assisted national tuberculosis programs, it has been observed that both the perceived effectiveness of treatment and individual and group education of patients during the initial intensive phase of short-course chemotherapy positively affected compliance during the continuation phase.

Other possible determinants of compliance include the number of medications taken at each time, the number of doses per week, and the cost of therapy to the patients. Combination tablets of isoniazid and thiacetazone and isoniazid and rifampicin have been in use in national tuberculosis programs of many developing countries for several years. Conversely, intermittent standard chemotherapy (streptomycin and isoniazid) has never been used on a large scale in developing countries. In India, it has been shown that intermittency leads to increased irregularity of compliance (Pamra and Mathur 1973). Also Blackwell (1979) could not validate the expected relationship between reduced number of doses and improved compliance. The advantages and disadvantages of intermittent standard chemotherapy will not be addressed further here. The common sense notion that increasing costs both in time and money will decrease compliance has been confirmed in most studies (Haynes 1979). To maximize compliance, tuberculosis chemotherapy should be free and the spatial and temporal ease of access to treatment should be improved. When alternative treatments are available in the private and public sector, patients may initially prefer to pay for therapy perceived as better, but when funds run out they may switch to the public sector (Uplekar and Shepard 1991). This mixing of different drug regimens will tend to increase the failure rate and the probability of secondary resistance.

The second factor determining the effectiveness is the development of drug resistance. Under ideal conditions, such as in many clinical trials in patients with sensitive bacilli, the cure rates for both standard and short-course chemotherapy are over 95 percent. In patients infected with tubercle bacilli that are isoniazid resistant, the cure rate with total compliance is greatly reduced (Shimao 1987). Isoniazid resistance is already a significant problem in many developing countries (Kleeberg and Boshoff 1980). A systematic application of short-course chemotherapy referred to above (2SHRZ/6TH) in new smear-positive cases makes it virtually impossible to select for a bacillus resistant to all four drugs. Decreased development of resistance means that short-course chemotherapy is a substantially more effective long-term strategy for tuberculosis control than standard chemotherapy. It has to be stressed that acquired (and in contacts of the index cases, primary) resistance to both isoniazid and rifampicin results in incurability of the majority of such cases in developing countries, with serious consequences for elimination of tuberculosis.

Finally, tuberculosis is maintained in the community by the transmission of the bacillus from smear-positive patients to susceptible hosts. Short-course chemotherapy converts most patients to smear negativity faster than standard chemotherapy and more effectively because of higher cure rates and higher compliance. Therefore, fewer patients transmit the bacillus to new hosts. Short-course chemotherapy will thus lead to a more rapid reduction in the risk of infection and incidence of clinical tuberculosis. This transmission effect for the treatment of smear-positive tuberculosis has a significant effect on the choice of chemotherapy.

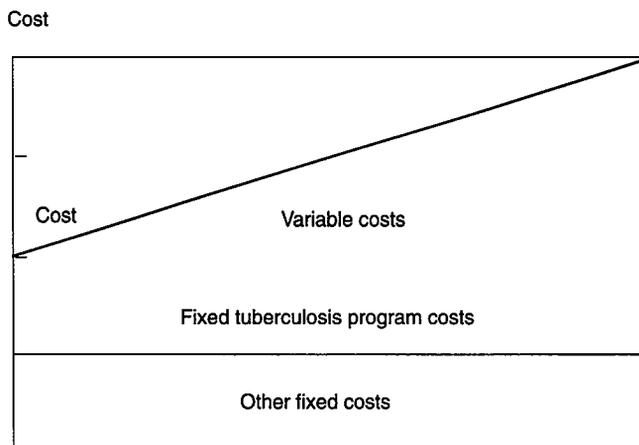
Costs of Chemotherapy

The cost of any tuberculosis control program is made up of the costs of many components, including drugs, staff, transportation, training, and hospitalization. Although drugs form a considerable portion of the budget, probably from 20 to 40 percent, they are not the only cost. Cost differences between short-course and standard chemotherapy, however, are attributable to the costs of drugs and hospitalization. The choice of suppliers, such as UNIPAC, Chinese pharmaceutical firms, or European companies, will have a substantial bearing on the costs of standard and short-course chemotherapy. Likewise, the size of the drug purchases have a significant influence on cost. Without a single agency or group that can evaluate the routine quality of antituberculosis drugs produced by different manufacturers, it is difficult to choose the most cost-effective supplier or suppliers. In general, the short-course regimen used in IUATLD national tuberculosis programs is approximately \$20 to \$25 more per patient than standard chemotherapy, depending on the supplier.

Another potential source of cost differences between treatment regimens is the level and intensity of supervision. Both standard and short-course chemotherapy should be given whenever possible on an entirely ambulatory basis. In some rural areas, however, where the population is without ready access to health facilities, daily regimens may have to be delivered in district hospitals to maintain acceptable compliance and cure rates. The experience of the national tuberculosis programs in Tanzania, Malawi, and Mozambique has indicated that hospitalization during the intensive phase of chemotherapy is indeed necessary in many areas. Not only will this improve compliance, but expensive and valuable drugs can be better accounted for in these conditions. Because two months of short-course chemotherapy can permanently cure more than 60 percent of patients as compared with standard chemotherapy, which cures only 30 percent, the higher cost of hospitalization may be more justified for short-course regimens in some circumstances.

This discussion has thus far been implicitly restricted to the treatment of smear-positive tuberculosis. Once other forms of tuberculosis have been identified, treatment costs for other tuberculosis should be similar to standard chemotherapy except for serious forms of smear-negative tuberculosis, such as miliary tuberculosis, tuberculous meningitis, Pott's disease,

Figure 11-11. Tuberculosis Program Costs



Source: Authors.

and so on. Those with these forms should be enrolled in short-course chemotherapy (patients with tuberculous meningitis should also be given rimactazid in the continuation phase of treatment). For treatment of cases in which the sputum or culture fails to convert in the first round of treatment, the drug costs are particularly high, because these patients harbor tubercle bacilli, frequently resistant, in developing countries, to isoniazid and/or streptomycin. Many of them have to be treated with short-course chemotherapy for retreatment cases, which should ideally contain three drugs to which the bacilli are sensitive. A retreatment regimen includes, as a rule, rifampicin and pyrazinamide. In the IUATLD-assisted national tuberculosis programs the following regimen is used: 2SHRZE/1HRZE/5H3R3E3 for patients resistant to isoniazid or 2SHRZE/1HRZE/5TH for patients sensitive to isoniazid. In programs that are committed to treating all patients that present for care, retreatment must also be considered in examining short-course and standard chemotherapy. Because failure rates are higher for standard chemotherapy, more resources would have to be devoted to retreatment of these patients.

Cost-Effectiveness

The cost-effectiveness of treating smear-positive tuberculosis will be addressed first. In general, the cost per death averted directly and indirectly will be lowest for smear-positive tuberculosis, higher for other tuberculosis, and highest for retreatment cases. Although this statement may run counter to intuitive notions of the clinical costs of treating each type of tuberculosis, the rationale is based on the effect of interrupting transmission, as explained more fully below.

Few studies have examined the cost-effectiveness of tuberculosis treatment in developing countries (Feldstein, Piot, and Sundaresan 1973; Barnum 1986; Joesoef, Remington, and Tjijtoherijanto 1989; Murray, Styblo, and Rouillon 1990). The authors of two of these investigations reported that per

case cured short-course chemotherapy was more cost-effective. They did not, however, report figures on the cost per death averted. To fill the gap in information on the cost-effectiveness of short-course and WHO standard chemotherapy, the national tuberculosis programs in Malawi, Mozambique, and Tanzania have been studied by Murray and others (1991) and DeJonghe and others (1992).

Before detailing the costs per case treated, some unit cost definitions are needed. Program costs in these three countries can be divided into three components. The first is variable costs, which are a direct function of the number of patients treated and include costs such as drugs, reagents for diagnosis, and food during hospitalization. The second component is the fixed costs associated with the tuberculosis program itself, such as the salaries of district and regional tuberculosis coordinators, capital costs of vehicles, and administrative costs of the tuberculosis unit. The third component is the fixed costs incurred through use of the primary health care infrastructure, such as clinics and district hospitals. These three types of costs are illustrated in figure 11-11. Three unit costs can also be defined. Marginal costs are here defined as the average variable costs per case; average incremental costs are variable costs plus the fixed tuberculosis program costs per case; and average costs are total costs, including the fixed costs outside the tuberculosis program per case.

Table 11-10. Estimated Costs per Case Treated in Malawi, Mozambique, and Tanzania
(1989 U.S. dollars)

Treatment and type of cost	Malawi	Mozambique	Tanzania
<i>Short-course chemotherapy with hospitalization^a</i>			
Average cost	160	217	174
Average incremental cost	99	155	127
Marginal cost	69	140	101
<i>Standard chemotherapy with hospitalization</i>			
Average cost	91	73	72
Average incremental cost	71	54	63
Marginal cost	42	40	37
<i>Ambulatory short-course chemotherapy</i>			
Average cost	66 ^b	55	50
Average incremental cost	45 ^b	36	41
Marginal cost	19 ^b	18	15
<i>Retreatment chemotherapy with hospitalization</i>			
Average cost	209	323	252
Average incremental cost	141	232	182
Marginal cost	97	206	146

a. Hospitalization for sixty days during the intensive phase of chemotherapy.

b. Hypothetical estimate based on measured costs; ambulatory therapy is not actually provided.

c. Hospitalization for ninety days.

Source: Authors.

Table 11-11. Estimated Average Incremental Cost per Patient Treated in Low- and Middle-Income Countries
(dollars)

GDP per capita	Short-course hospital ^a	Short-course ambulatory ^b	Standard hospital ^c	Standard ambulatory ^d
150	136	63	113	41
250	181	70	159	48
500	296	87	274	64
750	411	104	389	82
1,000	526	122	504	100
1,250	641	139	619	117
1,500	756	156	734	134

a. Short-course chemotherapy with sixty days of hospitalization during the intensive phase.

b. Short-course chemotherapy with daily supervision during the intensive phase.

c. Standard chemotherapy with sixty days of hospitalization during the intensive phase.

d. Standard chemotherapy with daily supervision during the intensive phase.

Source: Authors.

In table 11-10 we provide the estimated average, average incremental, and marginal costs per case treated under short-course, standard, and retreatment regimens for smear-positive cases with and without hospitalization. These costs cannot easily be generalized to developing countries that have substantially higher incomes per capita than those in Malawi, Mozambique, and Tanzania, whose gross domestic product (GDP) per capita is under \$300. Some treatment costs require foreign currency or are internationally traded goods; other costs are local costs that can be paid in local currency and are not traded commodities. By separating the external costs from the domestic costs, we can generate more representative estimates of the cost of treating patients in countries with different incomes per capita. The external component of the cost is assumed to be the same in all countries, whereas the domestic component is assumed to be proportional to GDP per capita. In table 11-11 we give our best estimates of the cost of chemotherapy in countries with different levels of income.⁷ Notably, the cost of chemotherapy with hospitalization increases much more rapidly than ambulatory strategies as GDP per capita increases. In other words, chemotherapy with hospitalization is relatively more affordable in low-income countries.

The benefits of chemotherapy can be divided into the direct benefits for the patient of cure and a reduced death rate and the indirect benefit of reduced transmission. A life table for the prognosis of smear-positive pulmonary tuberculosis based on the most detailed study of the prognosis of pulmonary tuberculosis by Berg (1939) is provided in table 11-12. The Bangalore epidemiological study confirms the general case-fatality rates in a developing country (Olakowski 1973; National Tuberculosis Institute, Bangalore 1974). For each program, the cohort results of chemotherapy have been used to construct an alternative life table of the fate of cases treated by the program. Comparison of the treatment life table and natural progression

Table 11-12. Life Table for Untreated, Smear-Positive Pulmonary Tuberculosis

Year after diagnosis	Population alive at beginning of year	Deaths during year	Population excreting bacillus at beginning of year
0	100,000	28,596	100,000
1	71,404	11,564	51,334
2	59,840	9,771	30,928
3	50,070	5,705	18,605
4	44,364	5,055	11,851
5	39,309	3,545	7,549
6	35,764	3,225	4,938
7	32,538	2,074	2,230
8	30,464	1,942	2,174
9	28,522	1,818	1,463
10	26,704	—	985

— Not available.

Note: Based on Berg's study of 6,162 cases. By convention, the radix of the starting population is set at 100,000.

Source: Berg 1939; authors.

life table allows us to quantify the marginal benefits of treatment. A model based on the principle that in an untreated population one case of tuberculosis will lead to one case of smear-positive tuberculosis in the future has been constructed. Transmission benefits have been counted for four transmission cycles, which occur over the next eighteen and one-half years. Deaths averted and years of life saved have been discounted at 3 percent. In the model, it is assumed that passive case detection will lead to diagnosis after three months of symptoms and that during the first three months before diagnosis the rate of transmission is 50 percent higher than normal. This captures the increased rate of transmission to close household contacts during the period before diagnosis. The false positive diagnosis rate has been studied in Tanzania and is less than 5 percent. The study results are based on an assumed false positive rate of 5 percent for all three programs.

The cost-effectiveness ratios for short-course and standard chemotherapy with and without hospitalization during the intensive phase are summarized in table 11-13. Four ratios are provided for each intervention: the cost per case cured; the cost per direct death averted; the cost per total death averted, which includes deaths averted due to decreased transmission over the next eighteen and one-half years; and the cost per year of life saved, including transmission benefits. Three conclusions follow from the cost-effectiveness ratios. First, chemotherapy for smear-positive tuberculosis is extremely cost-effective. The average incremental cost per year of life saved ranges from \$1 to \$4. Second, short-course chemotherapy is preferable to standard chemotherapy in virtually all situations. The ratios in table 11-13 show that short-course chemotherapy is cheaper than standard chemotherapy for virtually all indicators of cost-effectiveness. The absolute difference in the cost per unit benefit is not large, but the cost-effectiveness ratios do not tell the whole story. The cure rate with short-course chemotherapy in all three countries is approximately 25 percentage points higher than with standard chemotherapy. In

economic terms, the depth of the margin is much greater with short-course chemotherapy than with standard chemotherapy. There are also several other unquantified benefits to short-course chemotherapy. Rates of secondary resistance with short-course chemotherapy are much lower. And the cost of retreating failures has not been built into the comparison. With standard chemotherapy many more patients will require the expensive retreatment regimens. The benefits of short-course and standard chemotherapy are summarized in table 11-14.

We do not arrive at equally robust conclusions concerning the appropriate role of hospitalization with short-course chemotherapy. Clearly, ambulatory chemotherapy is much cheaper per patient treated. Experience in Tanzania and Mozambique has shown that in urban areas with good health service facilities high cure rates can be achieved with ambulatory short-course chemotherapy. In the rural areas, these same programs have not been successful in employing ambulatory

Table 11-13. Estimated Average Incremental Unit Costs per Case Cured and per Death Averted in Malawi, Mozambique, and Tanzania
(1989 U.S. dollars)

Treatment and type of cost	Malawi	Mozambique	Tanzania
<i>Short-course chemotherapy with hospitalization</i>			
Per case cured	165	232	202
Per direct death averted	200	267	236
Per total deaths averted	38	57	47
Per year of life saved	1.7	2.6	2.1
<i>Standard chemotherapy with hospitalization</i>			
Per case cured	215	301	270
Per direct death averted	187	272	227
Per total deaths averted	54	76	68
Per year of life saved	2.4	3.4	3.1
<i>Ambulatory short-course chemotherapy</i>			
Per case cured	107	81	101
Per direct death averted	130	94	117
Per total deaths averted	25	20	23
Per year of life saved	1.1	0.9	1.1
<i>Ambulatory standard chemotherapy</i>			
Per case cured	111	82	107
Per direct death averted	96	74	90
Per total deaths averted	28	21	27
Per year of life saved	1.3	0.9	1.2

Note: For Malawi, the estimates for standard chemotherapy with hospitalization and ambulatory short-course and standard chemotherapy are not based on actual program results. The costs are based on estimates of the likely cost of ambulatory chemotherapy, and the results of treatment are the average results achieved in Tanzania and Mozambique.

The results for ambulatory treatment are based on the overall results of the program for each country, not on specific results of ambulatory chemotherapy. They are applicable only to those urban areas where high compliance can be maintained with daily supervised chemotherapy in the intensive phase.

Source: Authors.

Table 11-14. Costs and Benefits of Short-Course Chemotherapy and Standard Chemotherapy Based on National Tuberculosis Programs of Malawi, Mozambique and Tanzania

Parameter	Standard chemotherapy	Short-course chemotherapy
Average incremental cost per year of life saved with hospitalization (U.S. dollars)	3.00	2.00
Cure rate	60	85
Percent of cases requiring retreatment (percent)	30	10

Source: Authors.

chemotherapy. Because the determinants of compliance are complex and often locally specific, we cannot make general conclusions. We can, however, estimate the marginal cost per patient cured through hospitalization for any given percentage point increase in the cure rate purchased through hospitalization during the intensive phase. In figure 11-12 we show, for Malawi, Mozambique, and Tanzania, the relation between the marginal cost per case cured and the absolute percentage point increase in the cure rate achieved through hospitalization. We show that once the cure rate is increased by as much as 10 to 15 percentage points, hospitalization becomes relatively inexpensive per marginal patient cured. In middle-income countries, where the cost of hospitalization increases much more than ambulatory chemotherapy, the increase in the cure rate would have to be substantially higher to achieve the same marginal cost per patient cured.

In countries with poorly trained microscopists or frequent atypical mycobacteria infections, the predictive value positive of sputum positivity could be lower than 95 percent. The potential of wasting scarce resources on patients without tuberculosis puts a high premium on training health workers and microscopists to diagnose tuberculosis correctly.

Chemotherapy for Smear-Negative Pulmonary Tuberculosis

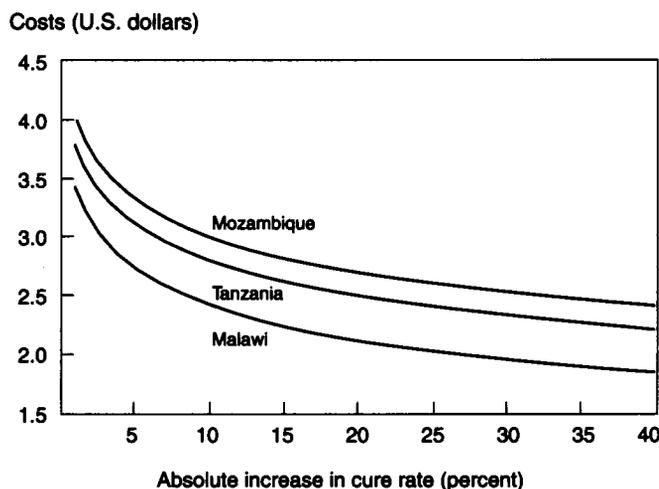
The cost-effectiveness of chemotherapy for smear-negative pulmonary tuberculosis is much more difficult to assess. The criteria both for diagnosis and effective therapy are less objective. A series of studies (see Toman 1979 for review and discussion) have shown that there is substantial variation in the x-ray diagnosis of active tuberculosis both between observers and by the same observer seeing the same film at different times. Cost-effectiveness can be discussed only in hypothetical terms and using realistic values from a variety of studies for the key parameters. There are four main determinants of the cost-effectiveness of chemotherapy for smear-negative pulmonary tuberculosis: the predictive value positive of x-ray diagnosis; the case-fatality rate of untreated smear-negative cases or cases suggested by x-ray; the effective cure rate of chemotherapy; and, perhaps most important, the percentage of tuber-

culosis cases diagnosed only by x-rays that would, if left untreated, progress to smear-positive tuberculosis.

The Bangalore epidemiological study provides one of the few sources for estimating these parameters (Olakowski 1973). Of 304 persons considered to have active or probably active tuberculosis according to radiological findings but who were smear and culture negative, a total of 13 percent became bacteriologically positive during five years of observation. If half of these were smear positive, that would be only 6.5 percent of those whose x-ray was suggestive of tuberculosis who went on to become infectious smear-positive patients. This percentage is the product of the specificity of the original x-ray diagnosis and the probability of true smear-negative persons progressing on to become smear positive. If diagnosis was only 50 percent specific, then 13 percent of the true smear negatives would have progressed on to become smear positive. This should be taken as the minimum estimate because smear-negative, culture-positive patients were excluded from the analysis. Short-course chemotherapy trials in Hong Kong have shown in a much more medically sophisticated setting that 56 percent of patients whose x-ray was suggestive of tuberculosis went on to develop bacteriologically positive or clinically active disease during a period of sixty months (Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council 1984).

In the Bangalore study, although the percentage becoming bacteriologically positive was low, the death rate of those whose x-ray was suggestive of tuberculosis was 30.9 percent over five years as compared with approximately 50 percent in bacteriologically confirmed cases. The mortality rate in the former cases was well over twice the baseline death rate in the study population.

Figure 11-12. Marginal Cost per Case Cured with Hospitalization and Short-Course Chemotherapy in Three Countries



Note: Costs are drawn on a log scale.
Source: DeJonghe 1993.

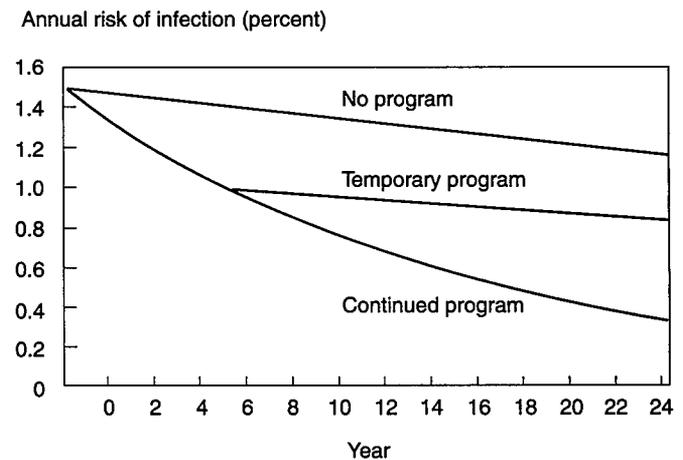
Using the average incremental unit cost for ambulatory therapy in Malawi, Mozambique, and Tanzania and a cheap short-course regimen for smear negatives (\$16 per course), we will calculate the hypothetical cost-effectiveness. We will assume a predictive value positive of 50 percent for active disease detected on x-ray. The true value will be locally specific and could well range between 25 and 75 percent. For true smear-negative cases, we will assume a case-fatality rate of 40 percent. Because the regimen proposed is ambulatory and the symptoms in smear-negative patients are often less severe, we will assume that the effective cure rate would be on the order of 50 percent. With this set of assumptions, the cost per death averted is \$450, or nearly ten times the cost per death averted of short-course chemotherapy with hospitalization for smear-positive patients and twenty times the cost of ambulatory short-course chemotherapy.

If a percentage of smear-negative cases do not progress to become smear-positive cases, then the costs of treating smear-negative patients are nearly an order of magnitude greater than the costs of treating smear-positive patients. On the basis of the Bangalore data, however, we expect that at least 10 to 15 percent would progress to become smear-positive patients. Treating smear-negative patients that go on to become smear positive cuts out the prediagnosis transmission that cannot be affected with chemotherapy for those who are smear positive. This prediagnosis transmission bonus accounts for nearly one-fifth of total transmission. If 15 percent of the cases progress to become smear positive, the cost per death averted by treating smear-negative patients is reduced to \$185 and \$155 if 20 percent become infectious. This is still three and one-half to eight times more expensive than treating smear-positive patients. In comparison with many other health sector interventions, this is relatively inexpensive per death averted or year of life saved. If the predictive value positive of x-ray diagnosis can be increased to 70 percent, the cure rate increased to 65 percent, and 20 percent of cases go on to be smear negative, the cost per death averted could be as low as \$85.

The Ratchet Effect

Investments in chemotherapy for smear-positive tuberculosis are relatively secure as compared with investments in other infectious diseases. An illustration of how chemotherapy programs can ratchet down the incidence of tuberculosis is presented in figure 11-13. The top line shows the slow decline in the annual risk of infection in the absence of an effective program. After twenty-five years the annual risk of infection will only be reduced by 20 percent. A good tuberculosis control program should be able to reduce the annual risk of infection by at least 6 percent per year—for example, since the 1950s, the annual risk of infection in the West has been declining by about 10 percent per year. If after seven years, as shown in figure 11-13, the program collapses, then the annual risk of infection will revert to its baseline rate of 1 percent decline. There is no reason to expect, as with malaria, schistosomiasis, or hookworm, that the risk of infection will increase back to

Figure 11-13. The Ratchet Effect



Source: DeJonghe 1993.

previous levels. The number of people infected by a smear-positive patient is a function of the social patterns of interaction and household structure, not of the overall risk of infection. The last line shows the rapid decline in the risk of infection if investments in chemotherapy are maintained. Each investment, even if only temporary, has a permanent effect of ratcheting down the annual risk of infection and thus incidence.

With the HIV epidemic, it is possible that the baseline decline in the annual risk of infection in Sub-Saharan Africa may not persist and may even be reversed. In this scenario, although the annual risk of infection will not be ratcheted down by investments in chemotherapy, there will be a persisting benefit. The two lines labeled “No program” and “Temporary program” in figure 11-13 would increase slowly at the same rate, maintaining a permanent difference in the ultimate risk of infection, even many years into the future.

BCG and Case Treatment

One would like to compare the two main interventions for tuberculosis control: BCG and case treatment. They are, however, not truly comparable because even complete BCG coverage at birth will affect only 4 to 7 percent of mortality. Case treatment is absolutely necessary to reduce the other 90 percent and more of mortality. How does the cost-effectiveness of expanding BCG coverage compare with expanding case-treatment activities? The cost per death averted can be compared directly using the studies mentioned earlier. Some may object that a death between the ages of 0 and 14 represents a greater loss of years of life than a death at age 35. If we choose to examine discounted years of life lost, however, it will not significantly alter the comparison. A death at age 7, the midpoint for deaths averted by BCG, represents, at a 3 percent discount rate, 29.7 years of life lost, whereas a death at age 34, the average age of a tuberculosis death, represents 23.4 years

at a similar discount rate. Therefore, we can examine the cost-effectiveness of the two interventions using the cost per death averted, bearing in mind that discounted years of life lost would change the relationship by less than 20 percent.

The cost per death averted through tuberculosis chemotherapy should change little as the risk of infection in a community declines. If all else remains the same, the only change would be the slight increase in the cost of detection as more cases of cough would have to be screened per case of tuberculosis detected. This does not hold true for any immunization, including BCG. The cost of immunizing all infants will not change as the risk of infection declines, but the benefits in terms of deaths averted will decline proportionately to the risk of infection. In other words, the cost per death averted through BCG must be inversely proportional to the risk of infection. In figure 11-7 we show two hypothetical curves for the cost per death averted as a function of the risk of infection. The curve for the cost-effectiveness of BCG is estimated on the basis of a single data point for Indonesia and the average cost per death averted for short-course chemotherapy with hospitalization during the intensive phase is based on data from Malawi, Mozambique, and Tanzania. Although the data are clearly weak, the principle is clear. At low annual risks of infection, case treatment is a substantially more cost-effective strategy than expanding BCG coverage. At higher risks of infection, the costs of both interventions are of the same order of magnitude. This curve should not be interpreted to mean that countries with low risks of infection should curtail BCG immunization activities. The discussion so far provides no insight into the savings from cutting back an existing activity as opposed to the potential reduction in benefits. This discussion does not imply that the policy choice in tuberculosis control is between BCG and case treatment. Some combination of the two is likely to be desirable in many countries. It does, however, indicate that BCG becomes relatively less attractive as the risk of infection declines.

Research Priorities

This discussion of tuberculosis leads naturally to some general recommendations for tuberculosis research. These can be divided into six areas.

EPIDEMIOLOGY. The wide confidence intervals in the estimates of incidence, prevalence, and mortality highlight the need for epidemiological research. Many countries require basic information on incidence and mortality rates and their distribution by age and socioeconomic status in order to establish the importance of tuberculosis as a health sector priority. For those countries that do not register vital statistics, new survey techniques based on the verbal autopsy may provide the tools with which tuberculosis mortality can be quantified.

PREVENTION. Because of the uncertain and variable effectiveness of BCG, a new effective vaccine would be an important

tool, especially if it also prevented tuberculosis in already infected individuals. Fine (1989), however, has pointed out that, for moral and technical reasons, it will be difficult to test appropriately the effectiveness of any new vaccines. Research is also needed to explore the most appropriate role for chemoprophylaxis in developing countries.

DIAGNOSIS. Development of new tools for the rapid diagnosis of tuberculosis would substantially improve case detection. Research into serological or sputum diagnosis that can be deployed in peripheral health facilities in developing countries should be a priority.

CHEMOTHERAPY. Development of new, shorter acting, cheap drugs would help address two important issues in tuberculosis control: compliance and cost. Although opportunities exist for developing new drugs (Sensi 1989), relatively little research is under way. Another possibility that seems worth exploring is the use of depot preparations and four drug combination pills which could solve compliance problems.

PROGRAM DESIGN. There is an urgent need for operational and health economics research on strategies for tuberculosis control. Some key issues have been highlighted in this chapter: what is the tradeoff between the cost of supervision and the improvement in compliance, taking the existing infrastructure into consideration? What is the cost-effectiveness of alternative diagnosis strategies? These and many other issues need to be addressed in an organized fashion.

HIV AND TUBERCULOSIS INTERACTIONS. The interaction between HIV and tuberculosis has not been fully addressed in this chapter. It appears that immune-suppressed patients with HIV have a high probability of developing clinical tuberculosis. In Central and East Africa, tuberculosis programs are already reporting an increase in the number of cases of tuberculosis. The effect of any HIV-tuberculosis interaction on the annual risk of infection for the rest of the population is not known. Epidemiological study of these relationships has just begun and should be considered a priority for research.

Major Operational Conclusions

This review of tuberculosis can be summarized in six main points.

- The magnitude of the tuberculosis problem is simply staggering. Our estimates suggest that 2.7 million people die from tuberculosis each year. This is probably more than from any other single pathogen. The burden of tuberculosis extends beyond morbidity; the annual incidence of new cases of all forms of tuberculosis is over 7.3 million in the developing world. Tuberculosis is unique among the main killers of the developing world in that it afflicts nearly all age groups. Many children die from tuberculous meningitis and miliary tuberculosis. But the greatest burden of tuberculosis

incidence and mortality is concentrated in adults age fifteen to fifty-nine. These are the parents, workers, and leaders of society. This heavy toll of the care givers makes tuberculosis a unique problem.

- In at least the last decade and a half, tuberculosis has been ignored by much of the international health community. Shimaō (1989) has outlined the decline of the human and institutional capacity to address the tuberculosis problem over the last decades, which is but one symptom of a general lack of priority attached to tuberculosis action and research. Another example is the study done by the Institute of Medicine (1986) of vaccine development priorities for the developing world. The institute classified diseases into three levels of priority for research on vaccines. Whereas leprosy received significant attention, tuberculosis was not even mentioned in the lowest priority group. Clearly, focusing international attention on tuberculosis is the necessary first step if more resources are to be directed to combatting the disease.
- Existing diagnostic technology and chemotherapeutic agents can be used effectively in developing countries to cure tuberculosis. The IUATLD-assisted national tuberculosis programs (for example, those in Malawi, Mozambique, and Tanzania) have shown that short-course chemotherapy can be applied on a national scale with excellent results. Cure rates approaching 90 percent, even taking into consideration problems with compliance, can be achieved in the most difficult circumstances.
- Short-course chemotherapy and BCG immunization (in countries with high risks of infection) are some of the most cost-effective health interventions available in the health armamentarium. The analysis of the programs in Malawi, Mozambique, and Tanzania has shown that treating smear-positive tuberculosis costs \$20 to \$57 per death averted. The cost per discounted year of life saved is therefore \$1 to \$3. There are few interventions that are as cost-effective as tuberculosis case treatment.
- On the basis of country-by-country estimates, taking into consideration the estimated incidence and current levels of case detection and treatment, we estimate that \$150 million in extra resources is needed to treat 65 percent of smear-positive patients in low-income countries and 85 percent of smear-positive cases in middle-income developing countries with short-course chemotherapy. Of this \$150 million, approximately \$70 million in foreign currency is required to address the problem of smear-positive tuberculosis.
- Evidence has accumulated that the interaction between HIV and tuberculosis may significantly exacerbate the epidemiological situation of tuberculosis. The potential rise, as a result of this interaction, in the risk of infection in Africa and other regions, depending on the spread of HIV, makes our operational conclusions about tuberculosis all the more pressing.

The combination of the enormous burden of the disease, years of neglect, the existence of effective interventions, and the availability of one of the most cost-effective interventions must make tuberculosis one of the highest priorities for action and research in international health.

Notes

1. The linear relationship between the annual risk of infection and the incidence of smear-positive tuberculosis will not hold at low annual risks of infection. As the annual risk of infection declines, the percentage of cases resulting from endogenous reactivation that are related to past levels of the annual risk of infection (during the last fifty to ninety years) rather than to current levels will increase.
2. There are two other problems with the interpretation of reported newly registered cases. For most countries, no distinction is provided between smear-positive cases and other cases. For countries in Latin America, the Middle East, and China, where a substantial portion of diagnosis is through x-ray, the numbers detected can be misleading. For example, in China, the widespread use of x-ray for diagnosis and the poor quality of microscopy means that only 10 to 20 percent of cases detected are smear positive. Many of the undetected smear-positive cases are probably diagnosed as smear negative with tuberculosis suggested by the x-ray. Many of the putative smear-negative cases, however, are probably misdiagnosed or overdiagnosed. Thus, if the total number of cases detected is divided by the estimated incidence, we will substantially overestimate case-detection rates. On the basis of discussions with national programs, we have adjusted the cases reported by China to reflect the likely overdiagnosis of smear-negative cases; data presented in Fox (1990) have been used to adjust the Indian data.
3. The midpoint of the confidence interval estimates is not equal to the expectation of the interval. When two 95 percent confidence intervals are multiplied, the resulting interval is actually much larger. In addition, the expectation is slightly lower than the interval midpoint.
4. If the age-specific case-fatality rate for ages twenty-five through twenty-four is assumed to be indexed at 1, then the other rates are: zero through fourteen, 0.9; fifteen through twenty-four, 1.15; twenty-five through thirty-four, 1.0; thirty-five through forty-four, 1.07; forty-five through fifty-four, 1.15; fifty-five through sixty-four, 1.65; and sixty-five and over, 2.5. The ratios for ages fifteen through sixty-five and over are based on Berg (1939); the ratio for ages zero through fourteen is based on case registration and tuberculosis mortality data for London during 1933–34 in Styblo (1984).
5. All dollar amounts are 1986 U.S. dollars.
6. The studies cited refer to the risk of developing clinical tuberculosis soon after primary infection. What about the risk of persons infected with tubercle bacilli developing clinical tuberculosis, with or without a fresh reinfection? Because it is not possible to detect reinfection with tubercle bacilli by tuberculin testing, it cannot be discovered directly whether or not exogenous reinfection is important in the development of tuberculosis in an adult. It is evident that in countries with low annual risks of infection, tuberculosis in elderly and old persons is predominantly a result of endogenous exacerbation among those remotely infected with tubercle bacilli. In developing countries, exogenous reinfection seems to play an important role in developing active tuberculosis in the adult population, because 0.5 to 2.5 percent or more of previously infected individuals are annually reinfected with tubercle bacilli, as was the case in industrial countries some two to four decades ago (Canetti 1972; Jancik and Styblo 1976). Strong evidence for the latter is the rapid decline in tuberculosis incidence in Eskimos over the space of twenty years, not only in children and young adults but also in elderly and old people, when aggressive case detection and adequate chemotherapy was introduced (Grzybowski, Styblo, and Dorken 1976).
7. This method is a modification of that of Barnum and Greenberg in chapter 21, this collection, who have calculated unit costs by the percentage of GDP per capita. External costs or the costs of internationally traded goods

whether they are domestically produced or not will not vary in proportion to GDP per capita. Local costs of nontraded goods, most notably labor, will in all probability change in proportion to GDP per capita. The distinction between external and domestic costs not only leads to different estimates of unit costs but can alter the relative cost of different interventions. As discussed in the text, the cost of an intervention with a higher domestic percentage of total cost will rise at a faster rate than the cost of an intervention with a higher percentage of external costs. Thus in a low-income country one intervention with a large domestic component may be cheaper than an alternative with a large external component. The relative cost-effectiveness rank could, however, reverse as income per capita rises.

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