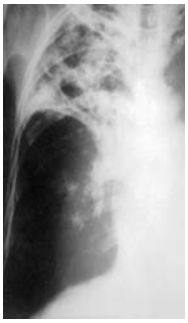
Part **Two**

Selecting Interventions

- Infectious Disease, Reproductive Health, and Undernutrition
- Noncommunicable Disease and Injury
- Risk Factors
- Consequences of Disease and Injury

Chapter **16**

Tuberculosis



Christopher Dye and Katherine Floyd

Despite the availability of drugs to cure tuberculosis (TB) since the 1940s, TB remains an important cause of death from an infectious agent, second only to the human immunodeficiency virus, or HIV (WHO 2004f). TB control is high on the international public health agenda, not only because of the enormous burden of disease, but also because short-course chemotherapy (SCC) is recognized as one of the most cost-effective of all health interventions (Jamison and others 1993). That recognition is partly attributable to an influential series of studies done in three of the poorest countries of southeastern Africa (Malawi, Mozambique, and Tanzania), which suggested that a year of healthy life could be gained for less than about US$5 (de Jonghe and others 1994; Murray and others 1991). This evidence has been central to the global promotion of the DOTS strategy, the package of measures combining best practices in the diagnosis and treatment of patients with active TB, in which direct observation of treatment during SCC is a key element (WHO 2002a, 2004c).

Although the World Health Organization (WHO) has fostered the implementation of DOTS over the past decade, four recent developments have drawn attention to a wider range of options for TB control:

- First, many more studies have investigated the costs, efficacy, and cost-effectiveness of different approaches to TB control. They are mostly studies of ways to improve the delivery of first-line drug treatment for active disease, but they include some investigations of preventive therapy (treatment of latent infection), treatment of multidrug-resistant TB (MDR-TB) using both first- and second-line drugs, and different approaches to diagnosis. They have been carried out in a variety of settings, in richer as well as poorer countries. The results have not been fully synthesized but may suggest ways to enhance DOTS.
- Second, striking increases in TB have been associated with the spread of HIV infection and drug resistance, suggesting that DOTS alone may not be enough to bring TB under control, especially in Africa and in the countries of the former Soviet Union.
- Third, there is now substantially more investment in new tools for TB control, including multimillion-dollar initiatives to develop better diagnostics, drugs, and vaccines, many of which operate under the umbrella of the Stop TB Partnership (see http://www.stoptb.org). Some of the possible products of this new research would stimulate reevaluations of the current reliance on chemotherapy, especially the development of a new high-efficacy vaccine.
- Fourth, interest in TB is renascent, not simply as the outcome of mycobacterial infection, but also as the consequence of exposure to exacerbating risks, such as tobacco smoke, air pollution, malnutrition, overcrowding, and poor access to health services. Research directed at quantifying these risks will also suggest ways to minimize them.

These developments set a big agenda for analysis. To make some inroads, this chapter presents an overview of the value for money and potential effect of the principal modes of TB control around the world. The starting point is a review of the natural history and clinical characteristics of TB and the geographical distribution of and trends in TB cases and deaths. This introduction sets the context for a discussion of the interventions that are now available to control TB and of how they have been used. We use a new method for evaluating the cost-effectiveness of infectious disease control and apply

this method systematically to four groups of TB interventions as they could be implemented in six regions of the world.

The internationally agreed-on targets for TB control, embraced by the United Nations Millennium Development Goals (MDGs), are to detect 70 percent of sputum-smear-positive cases and successfully treat 85 percent of such cases by the end of 2005. The expectation is that, if these targets can be reached and maintained, incidence rates will be falling by 2015, and the TB prevalence and death rates of 1990 will be halved by 2015. Meeting these targets requires a set of interventions that are not only cost-effective but also affordable and capable of having an effect on a large scale. The final sections of the chapter discuss the absolute costs and benefits of global TB control and the potential for achieving the effect defined within the MDG framework. The main themes of the text that follows are elaborated in a series of annexes available online at http://www.fic.nih.gov/dcpp as well as at http://www.who.int/tb/publications/en/.

TUBERCULOSIS INFECTION, DISEASE, AND DEATH

Human TB is caused by infection with mycobacteria, principally *Mycobacterium tuberculosis*. Individuals with pulmonary or laryngeal TB produce airborne droplets while coughing, sneezing, or simply talking. Inhaled infectious droplets lodge in the alveoli, and bacilli are taken up there by macrophages, beginning a series of events that results in either the containment of infection or the progression to active disease (Frieden and others 2003). Following uptake by macrophages, *M. tuberculosis* replicates slowly but continuously and spreads through the lymphatic system to hilar lymph nodes. In most infected people, cell-mediated immunity, associated with a positive tuberculin test, develops two to eight weeks after infection. Activated T lymphocytes and macrophages form granulomas, which limit the further replication and spread of bacilli. Unless a later defect occurs in cell-mediated immunity, the infection remains contained within the granulomas.

The immune mechanisms are, in their details, far more complex. For example, following antigenic challenge, a suite of different T cells is responsible for the induction and suppression of protective immunity, delayed hypersensitivity, cytolysis, and the production of antibodies and memory cells. Helper T cells mature into two functionally different populations: in *M. tuberculosis* infection, the T_H1 response is associated with granuloma formation and protection, whereas the T_H2 response results in tissue-necrotizing hypersensitivity and the progression of disease. The processes that determine the balance of the two responses affect, for example, the interaction between *M. tuberculosis* and other infectious agents (Grange 2003).

When the immune response cannot suppress replication, primary infection leads to active TB (progressive primary TB). The most common clinical manifestation is pulmonary disease, typically in the parenchyma of the middle and lower lung. In the most infectious patients, bacilli can be seen microscopically on stained sputum smears (60 to 70 percent of pulmonary cases; Marais and others 2004; Styblo 1991). Smear-negative patients may also be infectious but, per patient, contribute relatively little to transmission (Behr and others 1999; Hernandez-Garduno and others 2004). Extrapulmonary tuberculosis accounts for 10 to 30 percent of the disease but is more common among women and children (particularly lymphatic TB) and in people infected with HIV (Aaron and others 2004; Rieder 1999; Rieder, Snider, and Cauthen 1990; Shafer and Edlin 1996).

In the absence of other predisposing conditions, only about 5 percent of infected people develop progressive primary disease within five years of infection (Comstock, Livesay, and Woolpert 1974; Sutherland 1968, 1976). After five years, the annual risk of developing TB by the reactivation of latent infection is much lower($\approx 10^{-4}$ per capita per year). The risk of progressing to active disease is relatively high in infancy and lower in older children; it increases quickly during adolescence (earlier in girls) and then more slowly throughout adulthood (Comstock, Livesay, and Woolpert 1974; Nelson and Wells 2004; Sutherland, Svandova, and Radhakrishna 1982; Vynnycky and Fine 1997). Whether latent bacilli remain viable for the full life span of all infected people is unknown, but the risk of reactivation certainly persists into old age. The lifetime risk of developing TB following infection clearly depends on the prevailing transmission rate; the rule of thumb is 10 percent, but it has been calculated at 12 percent for all forms of pulmonary disease in England and Wales during the second half of the 20th century (Vynnycky and Fine 2000).

Besides the strong innate resistance to developing disease, infection is associated with an acquired immune response. This response is only partially protective (Dye and others 1998; Sutherland, Svandova, and Radhakrishna 1982; Vynnycky and Fine 1997), which helps explain why developing an effective vaccine has been difficult (few manufactured vaccines are more protective than natural immunity; Andersen 2001; Fordham von Reyn and Vuola 2002; Young and Stewart 2002). Consequently, individuals who carry a latent infection and who continue to be exposed are at risk of TB following reinfection. The importance of reinfection remains controversial, but mathematical modeling shows that the decline of TB in Europe cannot easily be explained without reinfection (Dye and others 1998; Vynnycky and Fine 1997). In addition, molecular fingerprinting has produced direct evidence that TB commonly arises from infection and reinfection in endemic areas (de Viedma and others 2002; Richardson and others 2002; van Rie and others 1999; Verver and others 2004), especially where subjects are infected with HIV (Glynn and others 2004).

The low incidence of infection and the low probability of breakdown to disease explain why TB is relatively rare. Its importance among infectious diseases is attributable not so much to the number of cases as to the high case-fatality rate among untreated or improperly treated patients. About two-thirds of untreated smear-positive patients will die within five to eight years, the majority within the first 18 months (Styblo 1991). Most of those who are still alive after eight years will have quiescent TB (self-cures, susceptible to relapse), and a few will become chronic excretors of bacilli. The case-fatality rate for untreated smear-negative cases is lower, but still of the order of 10 to 15 percent (Krebs 1930; Rieder 1999). Even among smear-positive patients receiving antituberculosis drugs, the case-fatality rate can exceed 10 percent if adherence to treatment is low or if rates of HIV infection and drug resistance are high (WHO 2004c).

Online annex 1 contains more information about factors that affect the risk to individuals of contracting infection and developing disease and the distribution of TB in populations.

EPIDEMIOLOGICAL BURDEN AND TRENDS

Surveys of the prevalence of infection and disease, assessments of the performance of surveillance systems, and death registrations yield an estimated 8.8 million new cases of TB in 2003, fewer than half of which were reported to public health authorities and WHO (online annex 2). Approximately 3.9 million cases were sputum-smear positive, the most infectious form of the disease (Corbett and others 2003; Dye and others 1999; WHO 2005). The African region has the highest estimated incidence rate (345 per 100,000 population annually), but the most populous countries of Asia harbor the largest number of cases: Bangladesh, China, India, Indonesia, and Pakistan together account for half the new cases arising each year. In terms of the total estimated number of new TB cases arising annually, about 80 percent of new cases occur in the top-ranking 22 countries.

In most countries (but not all), more cases of TB are reported among men than women. This differential is partly because women have less access to diagnostic facilities in some settings (Hudelson 1996), but the broader pattern also reflects real epidemiological differences between men and women, both in exposure to infection and in susceptibility to disease (Borgdorff and others 2000; Hamid Salim and others 2004; Radhakrishna, Frieden, and Subramani 2003). Where the transmission of *M. tuberculosis* has been stable or increasing for many years, the incidence rate is highest among young adults, and most cases are caused by recent infection or reinfection. As transmission falls, the caseload shifts to older age groups, and a higher proportion of cases comes from the reactivation of latent infection.

Globally, the TB incidence rate per capita appears to be growing slowly (online annex 2). Case numbers have been declining more or less steadily for at least two decades in Western and Central Europe, the Americas, and the Middle East. Striking increases have occurred in countries of Eastern Europe (mainly the former Soviet republics) since 1990 and in Sub-Saharan Africa since the mid 1980s, although trends in case notifications suggest that the rate of increase in both regions has slowed significantly since the mid 1990s (WHO 2005).

TB has increased in Eastern European countries because of economic decline and the general failure of TB control and other health services since 1991 (Shilova and Dye 2001). Periodic surveys indicate that more than 10 percent of new TB cases in Estonia, Latvia, and some parts of the Russian Federation are multidrug-resistant—that is, resistant to at least isoniazid and rifampicin, the two most effective anti-TB drugs (Espinal and others 2001; WHO 2004a). Drug resistance is likely to be a by-product of the events that led to TB resurgence in these countries, not the primary cause of it, for three reasons. First, resistance is generated initially by inadequate treatment caused, for example, by interruption of the treatment schedule or use of low-quality drugs. Second, resistance tends to build up over many years, and yet TB incidence increased suddenly in Eastern European countries after 1991. Third, although formal calculations have not been done, resistance rates are probably too low to attribute all of the increase in caseload to excess transmission from treatment failures.

Globally, 12 percent of new adult TB cases were infected with HIV in 2003, but there was marked variation among regions—from an estimated 33 percent in Sub-Saharan Africa to 2 percent in East Asia and the Pacific (online annex 2). HIV infection rates in TB patients have so far remained below 1 percent in Bangladesh, China, and Indonesia. The increase in TB incidence in Africa is strongly associated with the prevalence of HIV infection (Corbett and others 2002), and in populations with higher rates of HIV infection, women 15–24 years old constitute a higher proportion of TB patients (Corbett and others 2002). The rise in the number of TB cases in Africa is slowing, almost certainly because HIV infection rates are also beginning to stabilize or fall (Asamoah-Odei, Garcia Calleja, and Boerma 2004). HIV has probably had a smaller effect on TB prevalence than on incidence because HIV significantly reduces the life expectancy of TB patients (Corbett and others 2004). Where HIV infection rates are high in the general population, they are also high among TB patients; estimates for 2003 suggested that more than 50 percent of TB patients infected with HIV in Botswana, South Africa, Zambia, and Zimbabwe, among other countries.

Approximately 1.7 million people died of TB in 2003 (Corbett and others 2003), including 229,000 patients who were also infected with HIV (online annex 2). Although these

are usually reported as AIDS deaths under the *International Statistical Classification of Diseases and Related Health Problems, 10th revision* (ICD-10), and by WHO, TB control programs need to know the total number of TB deaths, whatever the underlying cause.

INTERVENTIONS AGAINST TUBERCULOSIS

TB can be controlled by preventing infection, by stopping progression from infection to active disease, and by treating active disease. The principal intervention is the DOTS strategy and its variations, centered on the diagnosis and treatment of the most severe and most infectious (smear-positive) forms of TB but including treatment for smear-negative and extrapulmonary cases as well. Anti-TB drugs can also be used to treat latent *M. tuberculosis* infection and active TB in patients with HIV coinfection, and the widely used bacillus Calmette-Guérin (BCG) vaccine prevents (mainly) severe forms of TB in childhood. These biomedical interventions directed specifically against TB can be implemented in a variety of ways through medical services and public action and can be supported by other efforts to reduce environmental risk factors (online annex 1).

Vaccination

Currently, the only means of immunizing against TB is with the live attenuated vaccine BCG, although other vaccines are under development (Fruth and Young 2004; Goonetilleke and others 2003; Horwitz and others 2000; Letvin, Bloom, and Hoffman 2001; Reed and others 2003; Young and Stewart 2002). Randomized controlled trials and case-control studies have shown consistently high protective efficacy of BCG against serious forms of disease in children (73 percent [95 percent confidence limits 67–79 percent] for meningitis and 77 percent [95 percent confidence limits 58–87 percent] for miliary TB) but highly variable—and often very low—efficacy against pulmonary TB in adults (Bourdin Trunz, Fine, and Dye, forthcoming; Fine 2001; Rieder 2003). Thus, even with the high coverage now achieved, BCG is unlikely to have any substantial effect on transmission. In parts of Europe and North America that did and did not use BCG, TB declined at rates that were not measurably different (Styblo 1991). In areas of high incidence, BCG vaccination is recommended for children at birth or at first contact with health services. Vaccination is being discontinued in many low-incidence countries because the risk of infection is low and because the response to BCG confounds the interpretation of tuberculin skin tests used to track persons infected during occasional outbreaks. BCG may have substantial nonspecific effects on child mortality—that is, in reducing deaths from causes other than TB—but this possibility is still controversial (Kristensen, Aaby, and Jensen 2000).

Reported BCG vaccination coverage has increased throughout the world during the past 25 years, reaching about 100 million infants, or 86 percent of all infants, in 2002. An estimated 92 percent of children were vaccinated in Europe and 62 percent in Africa in 2002 (WHO 2001). During the past 15 years, coverage has generally been most variable among African countries and least variable in Europe and the Americas. The most complete analysis of the effect of BCG vaccination suggests that BCG given to children born in 2002 prevents about 29,700 cases of childhood meningitis and 11,500 cases of miliary TB during the first five years of life, or one case for every 3,400 and 9,300 vaccinations, respectively (Bourdin Trunz, Fine, and Dye, forthcoming).

Treatment of Latent Infection

Individuals at high risk of TB who have a positive tuberculin skin test but not active disease (for example, associates of active cases, especially children and immigrants to low-incidence countries) can be offered treatment for latent TB infection (TLTI), most commonly with the relatively safe and inexpensive drug isoniazid. Studies among those who have contacts with active cases have demonstrated that 12 months of daily isoniazid gives 30 to 100 percent protection against the development of active TB (Cohn and El-Sadr 2000; Comstock 2000). For patients who may be carrying a strain resistant to isoniazid, rifampicin daily for 4 months is an acceptable alternative (or rifabutin, if used with protease inhibitors for HIV-infected people; Cohn 2003; Menzies and others 2004). Nevertheless, TLTI is not widely used. The main reason is that compliance with long-term daily treatment tends to be poor among healthy people—a relatively high risk of TB among those who are latently infected is usually still a low risk in absolute terms. An additional reason is that the tuberculin skin test tends to be less specific when applied to individuals who have been vaccinated with BCG. Although it is sometimes possible to make separate estimates of the number of individuals in a population who have been infected and who have received BCG (Neuenschwander and others 2002), distinguishing the responses to BCG and infection is harder in any given individual.

The exceptionally high risk of TB among persons coinfected with *M. tuberculosis* and HIV is a reason for encouraging wider use of TLTI, especially in Africa. However, there are significant barriers to making TLTI effective for coinfected individuals living in areas of high transmission (in addition to those listed earlier). Although trials of TLTI with individuals infected with HIV whose tuberculin skin test was positive have averaged about 60 percent protection for up to three years (with a good deal of variability), the effects have been lost soon afterward, and little or no effect has been seen on mortality (Bucher and others 1999; Johnson and others 2001; Mwinga and others 1998; Quigley and others 2001; Whalen and others 1997; Wilkinson,

Squire, and Garner 1998). In addition, identifying *M. tuberculosis* infection is more difficult in HIV-positive individuals than in those who are HIV-negative because the former are often anergic and are, therefore, unresponsive to tuberculin. Early studies have also experienced problems with uptake and compliance. In a pilot project in Zambia, for example, only 35 percent of HIV-infected individuals identified through HIV testing and counseling services actually started TLTI, and, of those who started, only 23 percent completed at least six months of treatment (Terris-Prestholt and Kumaranayake 2003).

TLTI has been used as a component of intensive, local control campaigns, such as those carried out for North American and Greenland Eskimos, but probably had effects secondary to the prompt treatment of active disease (Comstock, Baum, and Snider 1979; Styblo 1991). At present, TLTI plays no more than an accessory role in TB control in any setting, although the number of recipients around the world has been neither directly quantified nor indirectly estimated.

Treatment of Active Disease: The DOTS Strategy

The cornerstone of TB control is the prompt treatment of active cases with SCC using first-line drugs, administered through the DOTS strategy (WHO 2002a) within targets framed by the MDGs. The DOTS strategy has five elements:

- political commitment
- diagnosis primarily by sputum-smear microscopy among patients attending health facilities
- SCC with effective case management (including direct observation of treatment)
- a regular drug supply
- systematic monitoring to evaluate the outcomes of every patient started on treatment.

Standard SCC can cure more than 90 percent of new, drug-susceptible TB cases, and high cure rates are a prerequisite for expanding case finding. Although the DOTS strategy aims primarily to provide free treatment for smear-positive patients, most DOTS programs also treat smear-negative patients, usually without a fee. DOTS can be used as the basis for more complex TB control strategies where rates of drug resistance or HIV infection are high.

Mathematical modeling and practical experience suggest that the incidence of TB will decline at 5 to 10 percent per year when 70 percent of infectious cases are detected through passive case finding and 85 percent of these cases are cured, even though that level represents a treatment success rate among all infectious cases of only 60 percent (Dye 2000; Dye and others 1998). In principle, TB incidence could be forced down more quickly, by as much as 30 percent per year, if new cases could be found soon enough to eliminate transmission. In general, the decline will be faster where a larger fraction of cases arises from recent infection (that is, in areas where transmission rates have recently been high) and slower where there is a large backlog of asymptomatic infection. As TB transmission and incidence go down, a higher proportion of cases comes from the reactivation of latent infection and the rate of decline in incidence slows. These facts explain why it should be easier to control epidemic than endemic disease: during an outbreak in an area that previously had little TB, the reservoir of latent infection will be small, and most new cases will come from recent infection.

In the control of endemic TB, largely by chemotherapy, the best results have been achieved in communities of Alaskan, Canadian, and Greenland Eskimos, where incidence was reduced at 13 to 18 percent per year from the early 1950s (Styblo 1991). Over a much wider area in Western Europe, TB declined at 7 to 10 percent per year after drugs became widely available during the 1950s, although incidence was already falling at 4 to 5 percent per year before chemotherapy (Styblo 1991). More recently, between 1994 and 2000, the incidence of pulmonary TB among Moroccan children 0 to 4 years of age fell at more than 10 percent per year, suggesting that the risk of infection was falling at least as quickly (S. Ottmani, personal communication 2005). The overall reduction in pulmonary TB was only 4 percent per year, in part because of the large reservoir of infection in adults. DOTS was launched in Peru in 1991, and high rates of case detection and cure appear to have pushed down the incidence rate of pulmonary TB by 6 percent per year (Suarez and others 2001). For epidemic TB, as a result of aggressive intervention following an outbreak in New York City, the number of MDR-TB cases fell at a rate of more than 40 percent per year (Frieden and others 1995).

Although the long-term aim of TB control is to eliminate all new cases, cutting prevalence and death rates is arguably more important. About 86 percent of the burden of TB, as measured in terms of disability-adjusted life years (DALYs) lost, is attributable to premature death rather than illness, and prevalence and mortality can be reduced faster than incidence in chemotherapy programs. Thus, the TB death rate among Alaskan Eskimos dropped at an average of 30 percent per year in the period 1950–70 and at an average of 12 percent per year throughout the Netherlands from 1950 to 1990. Indirect assessments of the effect of DOTS suggest that 70 percent of the TB deaths expected in the absence of DOTS were averted in Peru between 1991 and 2000, and more than half the TB deaths expected in the absence of DOTS are prevented each year in DOTS provinces of China (Dye and others 2000; Suarez and others 2001). There have been few direct measures of the reduction in TB prevalence over time, but surveys done in China in 1990 and 2000 showed a 32 percent (95 percent confidence limits 9–51 percent) reduction in the prevalence rate of all forms of TB in DOTS areas, as compared with the change in the

prevalence rate in other parts of the country (China Tuberculosis Control Collaboration 2004; PRC Ministry of Health 2000). These findings imply that the targets of halving prevalence and death rates between 1990 and 2015 are technically feasible, at least in countries that are not burdened by high rates of HIV infection or drug resistance.

Many of the 182 national DOTS programs in existence by the end of 2003 have shown that they can achieve high cure rates: the average treatment success rate was 82 percent (that is, the percentage that were sputum-smear negative at the end of treatment plus the percentage that had completed treatment but for whom cure was not confirmed by sputum smear), not far below the 85 percent international target (WHO 2005). The outstanding deviations below that average were in Africa (73 percent) and some former Soviet republics (for example, 67 percent in Russia). Although the completion of treatment was almost a guarantee of cure before the spread of HIV and drug resistance, "completed" is an unsatisfactory way to report the outcome of treatment if cure is in doubt.

Although most TB patients probably receive some form of treatment, only 45 percent of all estimated new smear-positive cases were reported by DOTS programs to WHO in 2003. The case-detection rate in DOTS programs has been accelerating globally since 2000, but the annual increment must be still greater if the 70 percent target is to be reached by the end of 2005. Observations on the way DOTS is presently implemented suggest that a ceiling on case detection might be reached at about 50 to 60 percent (Dye and others 2003; WHO 2005). This fraction is about the same as the percentage of all cases reported annually to WHO from all sources (that is, from DOTS and non-DOTS programs). The problem is that, as DOTS programs have expanded geographically, they have not yet reached far beyond existing public health reporting systems.

ALTERNATIVE AND COMPLEMENTARY APPROACHES TO THE DIAGNOSIS AND TREATMENT OF ACTIVE DISEASE

The limitations of the DOTS strategy have stimulated numerous initiatives to improve program performance (including treatment protocols for patients carrying drug-resistant bacilli or who are infected with HIV), active case finding, collaborations within and between public and private sector health services, schemes for outpatient and community-based treatment, and integration of the management of TB and other illnesses.

Management of Drug-Resistant Disease

The higher the proportion of patients carrying drug-resistant bacilli is, the greater the need for accurate resistance testing and for the provision of alternative regimens that include at least three drugs to which bacilli are fully susceptible. Of greatest importance is resistance to the two principal first-line drugs, isoniazid and rifampicin (that is, MDR-TB). The introduction of resistance testing, second-line drugs, longer treatment regimens (12 to 18 months), and rigorous bacteriological and clinical monitoring all increase program costs without necessarily ensuring high cure rates (equal to or greater than 85 percent). Indeed, achieving the same cure rates for MDR-TB patients as for patients carrying fully susceptible strains may not be possible. The cost-effectiveness of this component of a TB control program is therefore lower by an amount that depends on the nature of the resistance, the methods of testing and monitoring, and the choice of regimen. The higher costs and lower cure rates associated with treating drug-resistant TB are part of the argument for preventing the spread of resistance in the first place, as can be investigated with models of selection and transmission (Dye and Espinal 2001; Dye and others 2002; Dye and Williams 2000). Suarez and others (2002) have investigated the cost-effectiveness of managing drug-resistant TB in Peru, but because studies in other settings have yet to be published, an empirical overview is not yet possible. Further data will be available from studies in Estonia, the Philippines, and Russia in 2005.

Treatment of HIV Coinfection

Antiretroviral therapy for HIV-positive individuals is unlikely to prevent a large fraction of TB cases unless treatment can be given shortly after HIV infection is acquired (Sonnenberg and others 2005; Williams and Dye 2003). In general, antiretroviral therapy is likely to be most effective, not in reducing TB incidence, but in extending the life expectancy of HIV-positive patients successfully treated for TB (Friedland and others 2004). Antiretroviral therapy and DOTS are formally synergistic, because without undergoing both together, HIV-infected TB patients have a short life expectancy, typically less than five years.

Where the prevalence of HIV infection has been rising quickly, as in eastern and southern Africa, even the most energetic programs of TB chemotherapy may not be able to reverse the rise in TB incidence. However, mathematical modeling indicates that, even in the midst of a major HIV epidemic, early detection and cure are the most cost-effective ways of minimizing TB cases and deaths (Currie and others, 2005). One reason is that DOTS programs treat all TB cases, not just those linked with HIV. The alternatives—the prevention of HIV infection, TLTI, and antiretroviral therapy—are less promising strategies to control TB, at least for the coming decade, although they could be used in combination with DOTS.

Active Case Finding

The DOTS strategy is based on passive case detection for three reasons: (a) the majority of incipient TB cases develop active

smear-positive, infectious disease more quickly than any reasonable interval between successive rounds of mass screening for TB symptoms or x-ray abnormalities; (b) the majority of patients severely ill with a life-threatening disease are likely to seek help quickly (Toman 1979); and (c) countries that have not yet implemented effective systems for passive case detection are not in a position to pursue cases more actively. The drawback of passive case finding is that the delays to diagnosis among symptomatic patients are often long, and health services never see some patients. To shorten delays and increase the proportion of cases detected, studies of risk can identify subpopulations in which TB tends to be relatively common. Systematic surveys of these subpopulations for active TB may be logistically feasible and affordable. The target populations include individuals infected with HIV, refugees (Marks and others 2001), contacts of active cases (Claessens and others 2002; Noertjojo and others 2002), health workers (Cuhadaroglu and others 2002), and drug users and prisoners (Nyangulu and others 1997). Despite the practical possibilities and the potential effect on transmission (Murray and Salomon 1998), active case finding is rarely done in high-burden countries, where the emphasis is still on implementing the basic DOTS strategy.

Case Finding and Treatment in the Private Sector

It is well known that many TB patients first seek treatment from private practitioners and that diagnosis and treatment in the private sector often do not meet internationally accepted standards (Uplekar, Pathania, and Raviglione 2001). A new scheme to deliver DOTS through the private sector (Public-Private Mix DOTS) operates through the provision of free drugs, by information exchange and patient referral, and with some financial support from participating governments. Two pilot projects in Hyderabad and Delhi, India, improved case-detection rates by 26 percent and 47 percent, respectively, and maintained treatment success close to the target of 85 percent (WHO 2004b). Other such projects are under way elsewhere in India as well as in Bangladesh, Indonesia, Nepal, the Philippines, and Vietnam (WHO 2004d).

Outpatient and Community-Based Treatment

Early studies of the cost-effectiveness of TB control found that full ambulatory treatment, eliminating hospitalization during the first two months (intensive phase), was cheaper and did not compromise cure rates (de Jonghe and others 1994; Murray and others 1991). Partly as a result, ambulatory treatment has become the standard of care in many high-burden countries. The natural extension, to home- and community-based treatment, has proved to be just as effective in several African settings, and even lower in cost (Adatu and others 2003; Dudley and others 2003; Floyd and others 2003; Floyd, Wilkinson, and Gilks 1997; Moalosi and others 2003; Okello and others 2003; Sinanovic and others 2003; Vassall and others 2002; Wilkinson, Floyd, and Gilks 1997). Various schemes have been used to provide TB care in the community, in which nongovernmental organizations, volunteers (Okello and others 2003), or appointed "guardians" (Floyd and others 2003) supervise treatment, sometimes with financial incentives (Sinanovic and others 2003). Consequently, community-based care is being adopted in some countries (for example, Uganda) as standard procedure.

Integrated Management of Tuberculosis and Other Respiratory Illnesses

Surveys in nine countries found that up to one-third of patients over five years of age attending primary health centers had respiratory symptoms, of whom 5 to 10 percent were TB suspects, but only 1 to 2 percent had TB (WHO 2004e). Because TB is rare among respiratory diseases, comanaging TB with other conditions has clear advantages. The purpose of the WHO's Practical Approach to Lung Health (PAL) project is to encourage a syndromic approach to management of patients, to standardize health service delivery through the development and implementation of clinical guidelines, and to promote the necessary coordination within national health services. Preliminary investigations in the Kyrgyz Republic and Morocco suggest that PAL projects can improve the accuracy of diagnosis, encourage better practice in prescribing drugs, and strengthen primary care. However, a full analysis of costs and effects in the nine-country study remains to be done.

COST-EFFECTIVENESS OF INTERVENTIONS AGAINST TUBERCULOSIS

Some questions about investing in TB control are broad and strategic (for example, should money be spent on the control of TB rather than on the control of some other condition?); others are specific and technical (for example, which laboratory diagnostic procedures should be used?). On whatever level the question is posed, cost-effectiveness analysis (CEA) has become a prominent method for evaluating and choosing among different health interventions.

Background

Between 1980 and 2004, 32 studies of the cost-effectiveness of TB control were published from the low- and middle-income countries considered by the Disease Control Priorities Project (table 16.1; online annex 3 summarizes the 32 studies that have been published according to the country and year of publication, the question being addressed, the strategies compared, the

Table 16.1 Number of Studies on the Cost-Effectiveness of TB Control by Topic and Region, 1980–2004

Intervention	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa	World	Total	Number that consider transmission
BCG vaccination	1	0	0	0	0	0	0	1	0
TLTI	0	0	0	0	0	3	0	3	3
Treatment of active disease: the DOTS strategy	4	2	0	1	0	2	0	9	4
Variations on DOTS:									
Management of drug-resistant disease	0	0	1	0	0	1	0	2	1
Treatment of HIV coinfection	0	0	0	0	0	1	0	1	0
Active case finding and diagnosis	0	1	1	0	0	4	1	7	1
Outpatient and community-based treatment	0	0	0	0	2	7	0	9	0
All interventions	5	3	2	1	2	18	1	32	9

Source: Authors.

subjects and costs considered, the effectiveness of measures used, whether or not transmission is considered, and the main results and conclusions). Almost all of these studies (28, or 88 percent) have concerned ways of finding, diagnosing, and treating patients with active TB, and most (18, or 56 percent) have been done in eight countries in Sub-Saharan Africa (Floyd 2003). Three studies (all in Sub-Saharan Africa) have investigated TLTI, and one study in Indonesia has examined BCG vaccination. The principal findings are that short-course chemotherapy for active TB is a comparatively cost-effective intervention and one of the most cost-effective of all health interventions. TB patients can be treated more cheaply and conveniently outside hospitals on an ambulatory basis, by health staff or with the help of family and community members, without compromising the success of treatment. Supplementary methods, such as standardized second-line drug treatment for MDR-TB, appear to be affordable and cost-effective in some settings.

What does not emerge from this compilation of data is a comprehensive overview of the value for money provided by current and potential interventions against TB in all major regions of the world, expressed using a common measure of effectiveness and based on a consistent approach to the evaluation of transmission. (The returns on investment in infectious disease control include the immediate benefits to individuals treated—for example, those vaccinated or given drug therapy—plus the longer-term benefits gained by preventing secondary cases through reduced transmission.) Little work has been done in China, India, and other large countries in Asia, even though Asia carries the largest burden of TB, and only limited information is available for Europe and Central Asia, Latin America and the Caribbean, and the Middle East and North Africa. Of the 32 studies, only 10 used a measure of effectiveness that allows comparison with other diseases (table 16.2), and only 9 attempted to include an estimate of the benefits gained from reduced transmission (table 16.1). The benefits from reduced transmission are usually assessed through mathematical modeling (using computer simulations) for a given epidemiological situation, an approach that produces specific solutions for each setting rather than results that are generally applicable. In addition, although the benefits from prevented transmission are lower when TB is endemic, existing studies do not make a clear distinction between the cost-effectiveness of interventions in epidemic (outbreak) and endemic situations.

Methods

In this study, a general analytical framework was used to evaluate the total costs and total effects (defined as cases prevented, deaths averted, and DALYs gained) of the principal interventions against TB across six regions of the world (see online annexes 4–7 for further details). A dynamic infectious disease model (online annex 4) was used to derive general formulas for calculating the cost-effectiveness of interventions

Table 16.2 Number of Studies on the Cost-Effectiveness of TB Control by Effectiveness Measure and Intervention, 1980–2004

Intervention	Cases detected or cases diagnosed	Cases prevented	Cure or successful treatment rate	Deaths prevented	Years of life saved	QALYs gained	DALYs gained
BCG vaccination	0	1	0	1	0	0	0
TLTI	0	3	0	0	0	1	0
Treatment of active disease: the DOTS strategy	0	1	6	1	3	0	1
Variations on DOTS:							
Management of drug-resistant disease	0	0	2	2	0	0	1
Treatment of HIV coinfection	0	0	0	1	0	0	0
Active case finding and diagnosis	5	0	0	0	1	0	2
Outpatient and community-based treatment	0	0	10	0	0	1	0
All interventions	5	5	18	5	4	2	4

Source: Authors.
QALY = quality-adjusted life year.
Note: The total for all interventions is greater than the number of studies because some studies use more than one measure of effectiveness.

to control endemic (online annex 5) and epidemic (online annex 6) TB in a wide variety of settings. The formulas are approximate, but they are simple and able to provide insights into the strategies that give value for money under a wide variety of epidemiological circumstances. The model was then supplied with cost and efficacy data (online annex 7) for each of the six World Bank regions for four main groups of interventions:

- immunization with BCG (proportion of infants, m, assumed to be protected against severe, noninfectious childhood TB only), or a new vaccine that prevents infection and progression to pulmonary and extrapulmonary TB in children and adults
- isoniazid treatment of latent TB infection (TLTI, given at per capita rate ρ), for people infected with *M. tuberculosis*, with or without HIV coinfection and with or without the use of radiography to exclude patients with active disease
- short-course chemotherapy, delivered as a component of the DOTS strategy, for smear-positive or smear-negative pulmonary disease and extrapulmonary disease (with a combination of drugs given at per capita rate τ), and for patients infected with HIV, with or without supporting antiretroviral therapy
- treatment for MDR-TB using a standardized regimen including first- and second-line drugs or using individualized regimens of first- and second-line drugs that are tailored to each patient's drug susceptibility pattern.

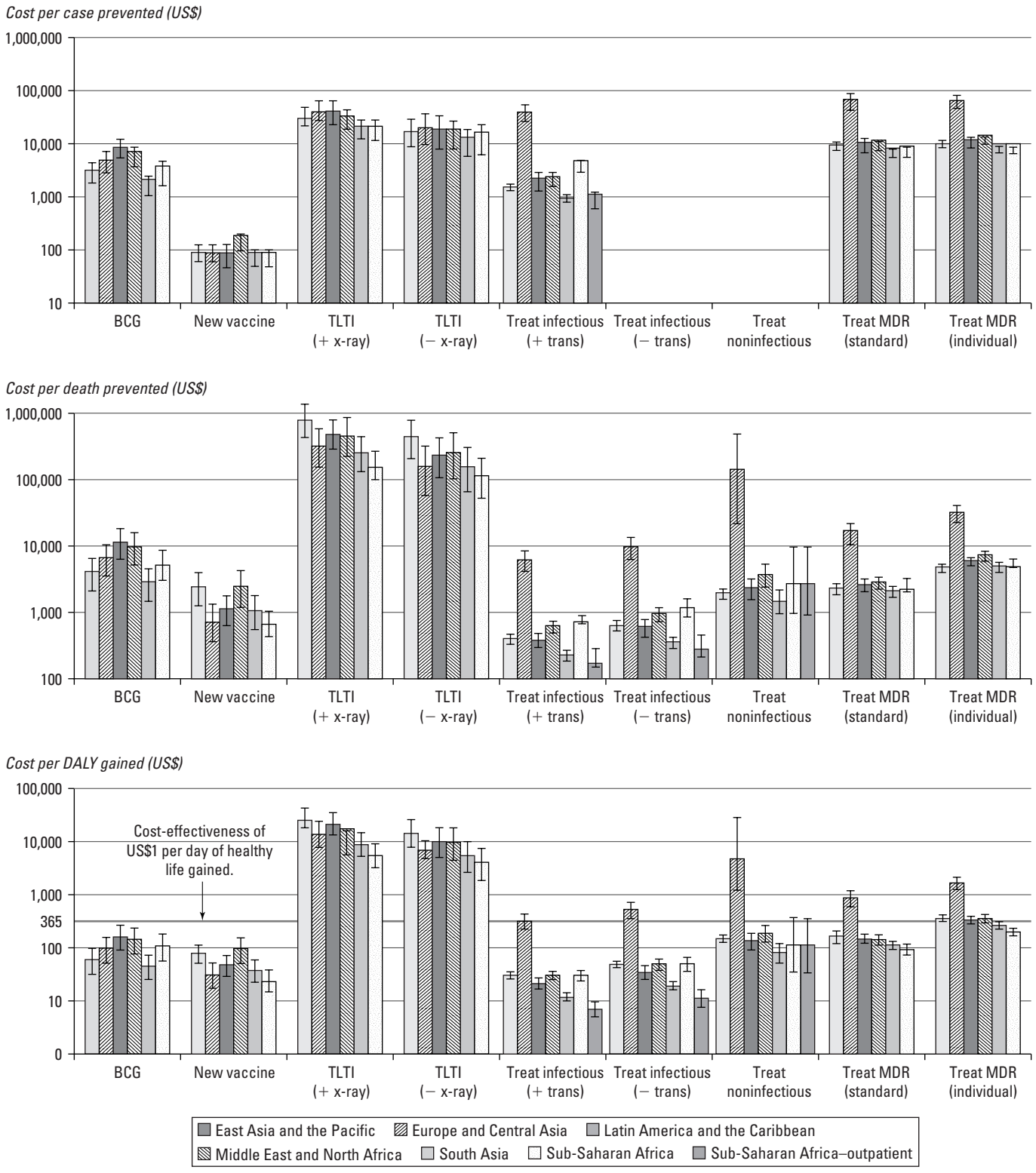
Costs were considered from a health system or provider perspective. They were calculated by combining estimates of the quantities of resources required for each intervention (per patient or per person treated) with the unit prices of those resources (in 2001 U.S. dollars) using the cost categories and unit prices defined in the Disease Control Priorities costing guidelines.

COST-EFFECTIVENESS OF MANAGING ENDEMIC TUBERCULOSIS

The primary problem in global TB control is the management of disease in countries where incidence has been roughly stable for many years (that is, where TB is endemic).

Cost per Case Prevented

In monetary terms, the cost-effectiveness (C/E) of a new program of treatment for active infectious disease (here defined as sputum-smear positive), per case prevented, can be calculated from $C/E \approx P/\epsilon kT$, where P is the cost of treatment, ϵ is the efficacy of treatment, k is a constant determined by the mode of action of the intervention, and T is the duration of the intervention in years (online annex 5). The cost per case prevented is mostly in the range of US$1,000 to US$10,000, depending on the region of the world (figure 16.1). The exception is Europe and Central Asia, where costs are high because patients are currently treated for long periods in hospitals rather than on an



Source: Authors.

Note: Where shown, bar 7 is for ambulatory (outpatient) treatment in Sub-Saharan Africa. The treatment of active disease saves no additional cases of TB when the effects of reducing transmission are excluded, so the cost per case prevented cannot be calculated. Cost-effectiveness of vaccination and TLTI is calculated for an initial incidence rate of 100 per 100,000 population per year. Cost-effectiveness ratios are plotted on a logarithmic scale. Error bars are 90 percent confidence limits. The horizontal gray line in the third chart marks a cost-effectiveness of US$1 per day of healthy life gained.

Figure 16.1 Cost-Effectiveness of Different Interventions against Endemic TB

ambulatory basis. These cost-effectiveness ratios (CERs) are computed from the total costs and total effects of treatment. Costs are therefore the same as the incremental costs for new programs. If costs and effects are compared with those of a previous treatment program, CERs for the treatment of active disease are often negative; that is, the program sooner or later saves money, as well as preventing TB cases. The positive CERs reported here for new treatment programs are, in this sense, upper estimates.

The cost of TLTI per active case prevented also depends on the initial incidence rate (I) and is calculated from $C/E \approx P/\epsilon kIT$ (online annex 5). The cost is substantially higher than that for the treatment of active TB: US$20,000 to US$40,000 when radiography is used to exclude patients with active disease, but it is less (US$13,000 to US$20,000) if active TB can be ruled out on the basis of symptoms and clinical examination (figure 16.1). TLTI is less cost effective than the treatment of active TB because preventive treatment would be given to latently infected individuals, most of whom were not recently infected and who are at small risk of developing active disease. In an endemic setting, there is no feasible method of identifying individuals who have recently acquired infection and who will proceed rapidly to active TB.

A new vaccine that prevents infection and, hence, the progression to pulmonary TB among people who were previously uninfected would be extremely competitive (US$90 to US$200) per case prevented if the costs were the same as those for BCG. BCG is cheap to manufacture and administer (US$1 to US$3 per dose) but less cost-effective (US$2,000 to US$8,500 per case prevented) than the treatment of active disease because it is assumed to protect against severe forms of childhood TB only and because it does not affect transmission (figure 16.1).

Cost per Death Prevented and DALY Gained

The wider benefits of treating active TB are revealed when allowing for the additional reduction in case fatality. For a 10-year program of treatment for infectious TB, the cost per death prevented is typically US$150 to US$750, and the cost per DALY gained is US$5 to US$50 for all regions except Europe and Central Asia (figure 16.1). When TB is close to the endemic equilibrium, the extra benefits gained from reducing transmission under DOTS are small: the cost per DALY gained is only 60 percent higher when transmission benefits are excluded. The treatment of noninfectious TB is less cost-effective (US$60 to US$200 per DALY gained), not primarily because transmission is unaffected, but because the case fatality of untreated smear-negative and extrapulmonary disease is relatively low. Treating infectious MDR-TB is between two and ten times more costly than treating drug-susceptible TB per death prevented (greater than US$2,000), or per DALY gained (greater than US$90), assuming resistant bacilli are as transmissible and pathogenic as susceptible bacilli.

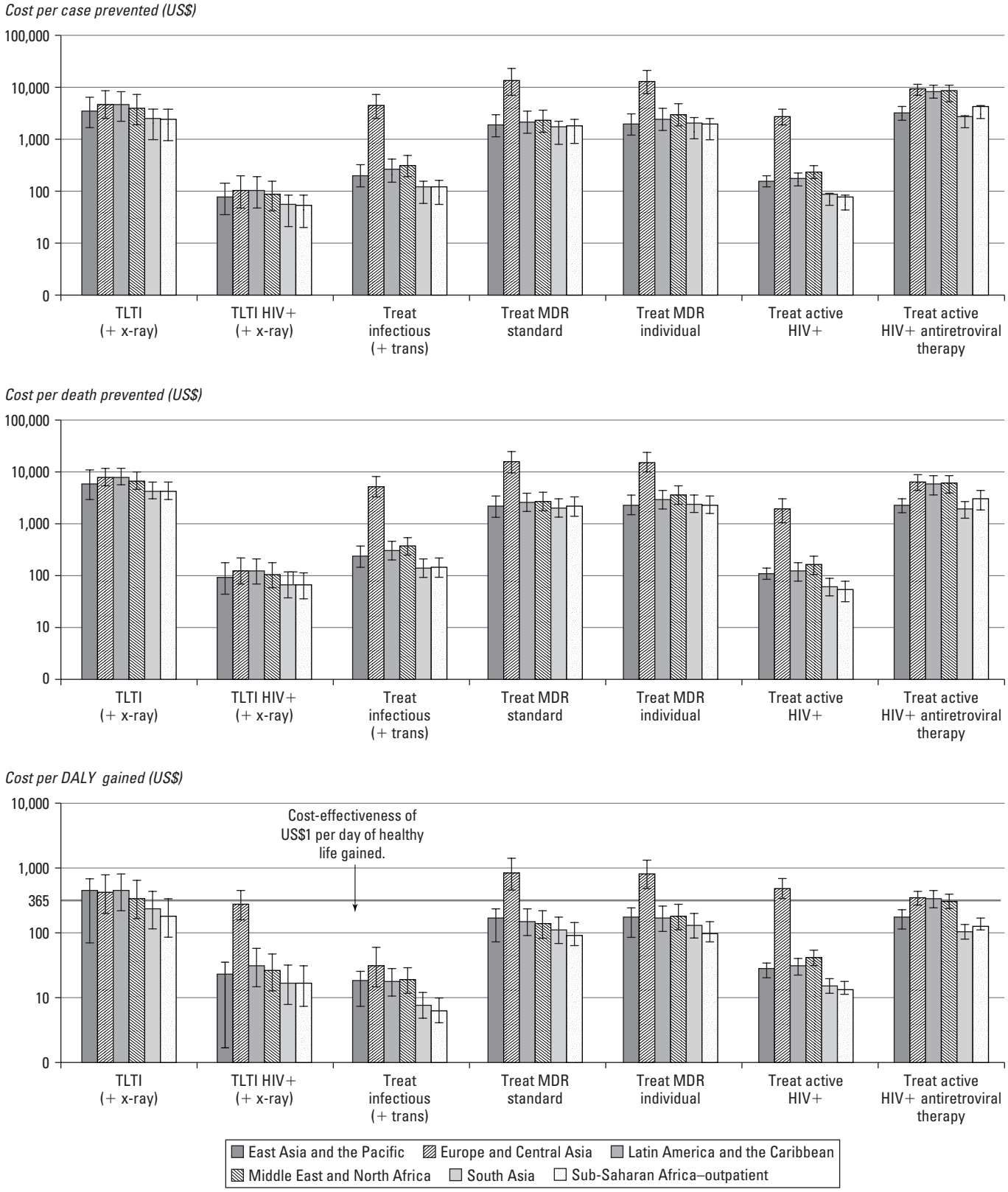
BCG vaccination is not much less cost-effective than the treatment of active disease (US$40 to US$170 per DALY gained; higher where the risk of infection is lower). If a new vaccine with 75 percent efficacy against pulmonary disease and other forms of TB costs the same as BCG, it would be almost as cost-effective (US$20 to US$100 per DALY gained) as the ambulatory treatment of active TB. As expected from the preceding analysis, TLTI is much more expensive than all other options (US$5,500 to US$26,000 per DALY gained) and most costly where the death rate from TB among adults is already relatively low—for example, because an effective DOTS program already exists. Although the cost-effectiveness of each intervention varies among regions, the variation among strategies is much greater, whatever the outcome measure (figure 16.1).

COST-EFFECTIVENESS OF MANAGING TUBERCULOSIS OUTBREAKS

The basic case reproduction number, R_0, is a ready-made epidemiological tool for relating effort and reward in the management of outbreaks. R_0 is the average number of secondary cases generated by a primary case introduced into a previously uninfected population (Anderson and May 1991). No country is presently free of TB, but some countries have recently suffered "epidemic" increases in incidence from previously low levels. The algebraic expression of R_0 for TB reveals how the various components of a disease's natural history and the different kinds of intervention interact with each other to influence transmission and the generation of new cases (online annex 4). For example, the cost-effectiveness of chemotherapy per *M. tuberculosis* generation is $C/E = P\sigma\tau/\epsilon R_0$, where τ is the number of TB patients treated per prevalent case per unit time, and σ is the proportion of new cases that is infectious.

The biggest resurgences of TB in recent history have been driven by the spread of HIV in Africa and are linked to the rise of drug resistance in former Soviet republics; this analysis is confined to interventions associated with these two phenomena (figure 16.2; online annex 6). Indeed, in this study, interventions related to TB with HIV are considered only in the epidemic context.

If multidrug-resistant strains of *M. tuberculosis* are assumed to have the same intrinsic transmissibility and pathogenicity as drug-susceptible strains, and given the spread of MDR-TB as an independent epidemic (Dye and Williams 2000), then treatment of MDR-TB with a standard regimen including second-line drugs is more costly per DALY gained than treatment of fully susceptible disease in Sub-Saharan Africa, but it is marginally less costly than TLTI (with an x-ray screen) over most rates of case detection and treatment (online annex 6).



Source: Authors.

Note: Five interventions used in the management of TB epidemics that are linked with HIV and MDR-TB (TLTI for people coinfected with TB and HIV, treatment of infectious MDR-TB with a standard or individual regimen, treatment of HIV-infected TB patients with TB drugs, treatment of HIV-infected TB patients with TB and antiretroviral drugs) are compared with two standard methods (TLTI, with active disease excluded by x-ray screen, and treatment of active infectious disease, allowing for transmission). Cost-effectiveness ratios (plotted on a logarithmic scale) vary with the treatment rate (online annex 6); for illustration here, 20 percent of eligible people are treated annually with each intervention. The horizontal gray line in the third figure marks a cost-effectiveness of US$1 per day of healthy life gained. Error bars are 90 percent confidence limits.

Figure 16.2 Cost-Effectiveness of Managing Epidemic TB

For example, at the fixed rate of treatment used to generate figure 16.2, treatment of MDR-TB with a standard regimen costs US$91 to US$846 per DALY gained, depending on the region, as compared with US$6 to US$31 for the treatment of drug-susceptible TB. The treatment of MDR-TB with regimens tailored to the resistance patterns of individual patients is more costly but also more efficacious than standardized treatment for MDR-TB and, therefore, almost equally cost-effective under this set of assumptions.

TB patients infected with HIV are more costly to treat per DALY gained than HIV-negative patients, either without antiretroviral therapy (low cost, short life expectancy) or with such therapy (high cost, long life expectancy). TLTI is a more attractive option for the management of epidemic TB than for endemic TB (compare figures 16.1 and 16.2), because during an outbreak, TLTI is directed at recent rather than remote infection. TLTI is even more cost-effective in the control of TB and HIV coinfection, because it prevents the rapid breakdown to active disease caused by immunodeficiency.

These results are indicative rather than definitive, because the calculations assume, among other things, that HIV-infected populations exist in isolation; in reality, HIV-infected people also acquire TB infection from TB patients who are not infected with HIV. Neither does this analysis address all the important questions about managing outbreaks of drug-resistant or HIV-related TB. Fuller investigations should assess, for example, the benefits to whole populations of giving antiretroviral therapy to HIV-infected individuals before they develop TB and of investing in DOTS to prevent multidrug-resistant epidemics from arising in the first place.

SUMMARY OF COST-EFFECTIVENESS ANALYSES

Box 16.1 summarizes the results of these calculations of the cost-effectiveness of managing epidemic and endemic TB. The findings are one justification for maintaining and expanding DOTS programs, on the basis of SCC for patients with active disease, as the dominant mode of TB control around the world. BCG vaccination and the treatment of MDR-TB (standard or individualized regimens) or HIV-infected TB patients (with or without supporting antiretroviral therapy) are more costly in absolute terms, but they typically cost less than US$1 per day of healthy life gained, which is less than the average economic productivity of workers in the least developed countries. TLTI appears to be relatively poor value for money, even though this analysis assumes that one course of treatment prevents active

Box 16.1

Cost-Effectiveness of TB Interventions: Main Findings

- The cost effectiveness of TB control depends not only on local costs but also on the local characteristics of TB epidemiology (for example, epidemic or endemic, low or high rates of HIV infection and drug resistance) and on the rate of application of any chosen intervention.
- Short-course chemotherapy for the treatment of infectious and noninfectious TB patients through the DOTS strategy is highly cost-effective for the control of either epidemic or endemic TB (US$5 to US$50 per DALY gained, for regions excluding Eastern and Central Europe). When a new treatment program is compared with a previous program, DOTS often saves money as well as preventing cases and deaths.
- Some variations on DOTS are less cost-effective but still good value for money, including the treatment of patients with MDR-TB (standard or individualized drug regimens) and with HIV infection (with or without supporting antiretroviral therapy). For these additional interventions, the cost per DALY gained is less than the annual average economic productivity per capita in the least developed countries.
- Even with relatively favorable assumptions, the treatment of latent TB infection where TB is endemic and populations are unaffected by HIV is the least cost-effective of the interventions examined here (US$5,500 to US$26,000 per DALY gained). TLTI is more cost-effective during outbreaks (US$150 to US$500 per DALY gained) and for people who are coinfected with TB and HIV (US$15 to US$300 per DALY gained).
- BCG vaccination to prevent severe forms of childhood TB is much less effective than SCC but nearly as cost-effective (US$40 to US$170 per DALY gained).
- A new vaccine that prevents pulmonary TB with high efficacy (equal to or greater than 75 percent) would be more cost-effective than BCG if the cost of immunization were the same as BCG (US$20 to US$100 per DALY gained).
- For any intervention with the potential to cut transmission (that is, excluding BCG vaccination), control of epidemic disease produces more favorable cost-effectiveness ratios than control of endemic disease, because the benefits gained from reduced transmission are greater during outbreaks.

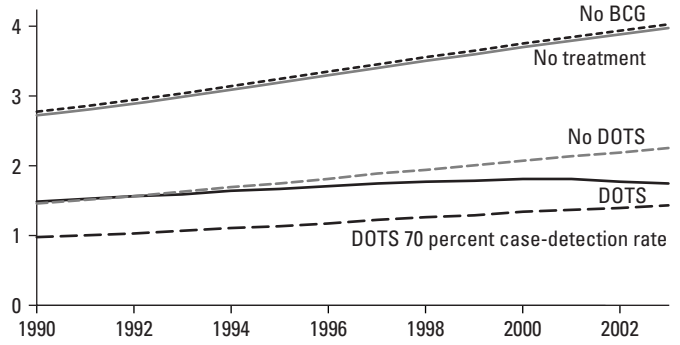
Source: Authors.

TB for life. TLTI is more cost-effective in epidemic than in endemic settings, and it is more cost-effective when it is used to treat individuals coinfected with TB and HIV. A new, high-efficacy vaccine that prevents infection and the progression to pulmonary TB in adults, to be directed at the control of endemic TB, would be more cost-effective than BCG at the same price and almost as cost-effective as SCC.

Averted and Avertable Burden of Tuberculosis

Trends in case notifications can be used, judiciously, to assess regional and global trends in TB incidence, but no satisfactory large-scale analysis has been done of the number of cases prevented by chemotherapy (as distinct from the reductions in transmission and susceptibility associated with improved living standards). One approach to evaluating the averted and avertable burden of TB begins with the observation that 86 percent of the years of healthy life lost that are attributable to TB are from premature death, and only 14 percent are from illness. Because DALYs lost are dominated by premature death, a conservative estimate of the burden of TB alleviated can be obtained in terms of the number of deaths and associated DALYs gained, regionally and globally, since the introduction of the DOTS strategy in 1991.

Figure 16.3 is derived from recent estimates of cases and deaths and their trends by region, including those attributable to HIV coinfection (Corbett and others 2003; WHO 2004c). In the MDG baseline year, 1990, approximately 1.5 million TB deaths (28 per 100,000) occurred. BCG vaccination saved roughly 650,000 deaths from extrapulmonary TB among children between 1990 and 2003. If chemotherapy is assumed to reduce only the case-fatality rate and to have no effect on transmission and incidence, 23 million deaths (44 percent) would have been saved in non-DOTS treatment programs. The expansion to 45 percent case-detection rate under DOTS during the same period saved an estimated 2.3 million (≈5 percent) additional deaths, the largest numbers in Sub-Saharan Africa (1.1 million), East Asia and the Pacific (558,000), and South Asia (408,000). Further analysis shows that, if 70 percent of TB cases (smear positive and smear negative) can be treated under DOTS before MDG target year 2015, an estimated 1.9 million TB deaths (26 per 100,000) will occur in that year, a greater number than in 1990, but a 7 percent lower death rate per capita (Dye and others 2005).



Source: Authors.

Note: Broken and gray lines represent various hypothetical scenarios; the solid black line represents DOTS programs. The interventions are, from top to bottom: no BCG vaccination and no anti-TB treatment, no treatment, no DOTS programs, DOTS expansion from zero to 45 percent case detection over the period 1990–2003, and DOTS with 70 percent case-detection rate throughout the period 1990–2003. To make a conservative assessment of effect, the treatment of active TB is assumed to change the case-fatality rate without affecting the TB incidence rate.

Figure 16.3 Estimated Number of TB Deaths Worldwide under Various Hypothetical Scenarios and the Estimated Effect of DOTS Programs, 1990–2003

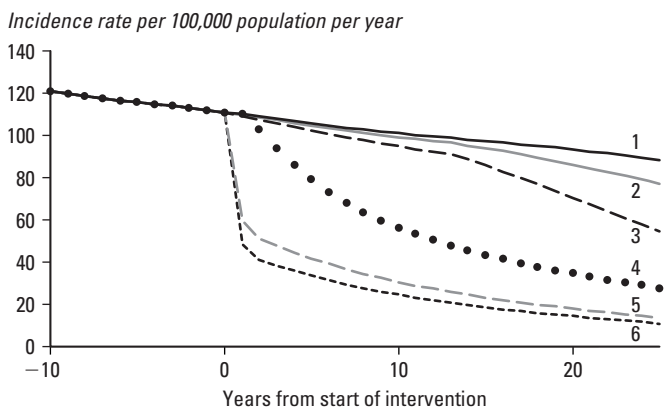
The calculations for Africa assume that treatment cures TB in the majority of HIV-infected patients even though, without antiretroviral therapy, many of these patients will die anyway. Despite these favorable assumptions, the number of TB deaths was evidently still rising in Africa in 2003, whereas it was falling in Asia, aided by the large programs of DOTS expansion in China (1991–97) and India (from 1998).

Reducing the TB death rate sufficiently to meet the MDG target requires a significant cut in incidence, as well as in case fatality. An extension of this assessment suggests that case detection must reach at least 70 percent and the TB incidence rate must fall by 5 to 6 percent annually between 2003 and 2015 (Dye and others 2005). For the world, excluding Sub-Saharan Africa and former Soviet republics, the incidence rate would have to fall at a more modest 2 percent per year.

New diagnostics, drugs, and vaccines would also help reduce the global TB burden more quickly. The most desirable of these is a vaccine that prevents pulmonary disease, whether or not vaccination subjects are already infected (a pre- or postexposure vaccine), and that confers lifetime immunity (Andersen 2001; Fordham von Reyn and Vuola 2002; McMurray 2003; Young and Stewart 2002). A new vaccine with high efficacy against pulmonary TB would almost certainly change immunization practice: mass vaccination campaigns among adults (rather than infants) would have dramatic effects, going far beyond the expectations of DOTS programs (figure 16.4; Dye 2000). A postexposure vaccine that stops progression to disease among those already infected, as well as preventing infection in others, would have greater effect than a preexposure vaccine that only prevents infection (Lietman and Blower 2000). However, such calculations are at present highly speculative, because the mode of action and efficacy of any new vaccine is unknown.

Economic Benefits of Tuberculosis Control

Preventing TB deaths brings no savings in the costs of TB control unless it is accompanied by a reduction in incidence so that fewer patients require treatment. The prompt and effective



Source: Dye 2000.

Note: Lines and points show: (1) no intervention in a population where TB is already in slow decline, as in many countries in Asia and Latin America; (2) a postexposure vaccine given annually to infected infants so that 20 percent are immunized; (3) a postexposure vaccine given annually to infected infants so that 70 percent are immunized; (4) DOTS reaching 70 percent case detection and 85 percent cure by year 5 and maintained at these levels thereafter; (5) one-time mass immunization with a preexposure vaccine giving 70 percent protection to uninfected people, followed by annual vaccination of infants with the same fraction protected; and (6) one-time mass immunization with a postexposure vaccine giving 70 percent protection to uninfected people, followed by annual vaccination of infants with the same fraction protected.

Figure 16.4 Hypothetical Effect of New Vaccines on TB Incidence Rate

treatment of active disease is almost certainly reducing transmission around the world, but because the effect on incidence is necessarily slow, it has been hard to quantify in all but a few countries, notably Peru (Suarez and others 2001).

The monetary savings implied by a reduction in incidence of one-quarter (26 percent) between 2000 and 2015—which may be enough to achieve the MDG targets—could be magnified or diminished by adjustments to the DOTS strategy. On the one hand, without compromising cure rates, chemotherapy can be delivered more cheaply to outpatients than inpatients and with less reliance on x-ray diagnosis and surgical procedures. On the other hand, various additions to DOTS—contact tracing, active case finding, antiretroviral therapy for HIV-infected patients, second-line drugs for patients carrying resistant bacilli, or joint public-private schemes for the management of TB—might be desirable but more costly per year of healthy life gained. Whether the savings made by reducing incidence and improving efficiency offset the costs of DOTS add-ons will, therefore, depend on the setting.

Besides the possibility of reducing diagnostic and treatment costs, improved health and longevity yield other economic benefits, but the quantification of those benefits is always controversial. This difficulty is reflected in the limited number of cost-benefit analyses of TB control; among the few examples, one detailed study in India estimated the potential societal benefits of DOTS to be worth US$8.3 billion in 1993–94, or 4 percent of the gross domestic product (Dholakia 1996). Without attempting to extend such analyses here, we note that the preceding results also imply that large-scale treatment programs for TB are likely to give net returns on investment or at least to appear to be good value for money in ways that go beyond the arguments from cost-effectiveness (Jack 2001).

The analysis earlier in this chapter showed that SCC typically costs up to US$30 per DALY gained for the treatment of infectious TB and up to US$200 per DALY gained for the treatment of noninfectious TB (excluding Europe and Central Asia). These figures can be compared with a recent estimate of US$1.5 billion as the annual global cost of treating 70 percent of cases with 85 percent cure (WHO 2004c). Reaching these targets would prevent approximately 2.1 million of all the TB deaths expected if no treatment were available in 2003, including 391,000 deaths prevented by DOTS (figure 16.3). Because each TB death prevented gains approximately 20 DALYs (WHO 2002b), the total cost per DALY gained would be about US$36. This rough calculation excludes any benefits in reduced transmission but includes the costs of treating smear-negative and extrapulmonary TB and is of the same order of magnitude as the results from CEA.

However the calculation is done, the cost of gaining a year of healthy life under DOTS is substantially less than the annual average productivity per capita in the low-income (gross national income [GNI] less than or equal to US$735) or least developed (GNI average US$290, http://www.worldbank.org) countries, and it is probably less than the marginal productivity of labor in the poorest communities. It is also less than twice the average annual income per capita, which has also been proposed as a benchmark for assessing whether an intervention is cost-effective (Garber and Phelps 1997). Moreover, it is less than the World Bank's definition of *absolute poverty* (living on US$1 per day or less, close to average GNI per capita for the least developed countries) and is certainly less than the monetary values that are typically placed on the value of a human life year (for example, a life was valued at US$100,000 by the 2004 Copenhagen Consensus panel, http://www.copenhagenconsensus.com). All these comparisons suggest not only that the basic DOTS strategy, and perhaps even an enhanced DOTS strategy, are cost-effective but that they also have very favorable cost-benefit ratios.

RESEARCH AND DEVELOPMENT

The preceding review and analysis suggest at least six areas for economic and epidemiological research and development:

1. *DOTS expansion.* Refinement of existing cost estimates of scaling up DOTS programs to reach and move beyond targets for case detection (70 percent) and cure (85 percent) in the poorest countries—notably in Africa—through more comprehensive planning and budgeting exercises. The analyses should include the costs of developing fully staffed

health services, with expanded and renovated infrastructure and improved management capacity where necessary, and the costs of the new initiatives that will be required to improve case detection and cure rates.

2. *Service delivery.* Assessment of the potential for health service restructuring to detect, diagnose, and treat TB patients more efficiently through syndromic management of respiratory diseases at primary health centers and through collaborations between public and private health services, between different parts of the public sector health service, and between TB and HIV/AIDS control programs.
3. *Complementary strategies.* Further investigation of the costs and effectiveness of strategies that are potentially complementary to DOTS, including active case finding and TLTI in high-risk populations, and the management of drug resistance and of patients infected with HIV.
4. *Impact and targets.* Evaluation of the actual and potential effects of the tools (mostly drugs) now being used for TB control. This research requires a better understanding of the ways human population density, age structure, migration, HIV coinfection, and drug resistance affect TB epidemiology. The analyses should check the internal consistency of international targets for the implementation and effect of chemotherapy programs, as defined by the MDGs. The analyses should also make better use of the rich body of routine surveillance data collected by all national TB control programs around the world.
5. *Risk factors.* Assessment of the reductions in TB cases and deaths that could be made by reducing exposure to environmental risk factors, notably indoor and outdoor air pollution, tobacco smoking, and malnutrition. These risk factors affect the establishment of infection, the progression to active disease, and the outcome of treatment.
6. *New diagnostics, drugs, and vaccines.* A sensitive and specific test for active TB that is cheap and simple to use at the first point of contact between patients and health services would be a major advance in diagnosis. Mycobacterial culture, which detects a higher proportion of active TB patients than sputum-smear microscopy, is a prerequisite for screening for drug resistance. However, present culture methods are slow, taking four to six weeks to obtain a result. Technology based on phage amplification and nucleic acid amplification can establish whether cultures are positive in days or hours, but this technology needs to be packaged for use in developing countries (Albert and others 2002, 2004; Johansen and others 2003; Woods 2001). The tuberculin skin test is being superseded in many developed countries by more specific methods for detecting infection (Doherty and others 2002; Pai, Riley, and Colford 2004). A test that can predict who will progress from latent to active disease, as yet hypothetical, would greatly increase the feasibility of treating latent infection.

Among a growing list of new vaccine antigens (Fruth and Young 2004), three of the most promising are now undergoing phase 1 safety trials in humans. One trial has evaluated mycobacterial antigen 85, delivered as a recombinant smallpox vaccine (Goonetilleke and others 2003). Another is testing a live attenuated BCG bacterium (rBCG30) that overexpresses antigen 85B protein and that provides guinea pigs with greater protection than BCG alone (Horwitz and others 2000). A third trial is assessing a fusion protein of two different antigens in adjuvant, referred to as Mtb72f, that is likely to be used as a booster to either BCG or rBCG30 (Reed and others 2003). Compounds that could form the basis of new drugs and new drug regimens include the nitroimidazopyran PA-824. Experiments with a mouse model of TB have shown that PA-824 has bactericidal activity similar to that of isoniazid and sterilizing activity that may rival that of rifampicin and that it is particularly active against dormant bacilli.

Among the most important recent discoveries is a diarylquinoline with a novel mode of action on the ATP synthase of *M. tuberculosis* that powerfully inhibits both drug-sensitive and drug-resistant strains of bacilli (Andries and others 2004). Alongside these laboratory studies, analytical and operational research are needed to find out what kinds of new tools will give the best returns on investment. Investigations of this kind will contribute to the introduction of new vaccines, drugs, and diagnostics and will inform the work of the Foundation for Innovative New Diagnostics (http://www.finddiagnostics.org), the Global Alliance for TB Drug Development (http://www.tballiance.org), and the AerasGlobal TB Vaccine Foundation (http://www.aeras.org).

CONCLUSIONS

After more than a decade of climbing incidence rates in Africa and former Soviet republics, the global TB epidemic appears once again to be on the threshold of decline. The spread of HIV and drug resistance, respectively, in those two regions has exacerbated the problems of TB control, but at the same time it has helped keep TB on the international public health agenda. The global incidence rate was still rising in 2003, but more slowly each year. This slowdown is not only (or even mainly) because of direct intervention through DOTS programs but because HIV epidemics are approaching peak levels in Africa and because incidence is now starting to fall again in some former Soviet republics, including Russia. Where TB incidence is already falling, prevalence and death rates should be dropping more quickly, although little evidence demonstrates this decrease yet.

The prompt diagnosis and treatment of active TB has been the mainstay of TB control and will continue to be so for the foreseeable future. Short-course chemotherapy, delivered

through the DOTS strategy, is, at typically US$5 to US$350 per DALY gained, the most cost-effective among current methods for the management of TB, and in most high-burden countries, the cost is toward the lower end of this range. A comparison of the costs of treating active TB with the costs of running a previous program suggests that DOTS could actually save money in the long run. In addition, DOTS provides an operational framework for the introduction of more specialized methods in certain risk groups. The extensions to DOTS investigated here include the treatment of MDR-TB with second-line drugs, preventive therapy (TLTI) during outbreaks and for people coinfected with *M. tuberculosis* and HIV, and antiretroviral therapy for HIV-infected TB patients. Those interventions cost more than the basic DOTS strategy but are still less than a dollar for each day of healthy life gained, which provides an economic argument for their integration into enhanced DOTS programs.

Although the analyses in this chapter show that DOTS and its extensions are good value for money, they conceal various features of health systems, as yet poorly defined, that may facilitate the implementation of treatment programs. For example, if broader investment in the health sector is needed before TB control programs can work in some parts of some countries, then the full cost of DOTS could be greater. By contrast, a more integrated approach to the management of TB and other respiratory diseases in primary health facilities could lead to cost savings. Those possibilities have not yet been investigated.

The only development that could radically alter the current approach to TB control—shifting the emphasis from cure to prevention—is the discovery of a new vaccine that protects adults against infectious pulmonary disease. Whether such a vaccine would be more or less cost-effective than BCG (US$40 to US$1,600 per DALY gained) depends on price and efficacy, but the potential epidemiological effect would be far greater than that of BCG, perhaps justifying mass adult vaccination. If research and development proceed according to plan, a new vaccine of some kind could be licensed between 2010 and 2015. New drugs and diagnostics should be available earlier, shortening the delay to, and duration of, treatment.

Although cost-effectiveness studies show that DOTS is a good investment, they do not formally show that the strategy is affordable. The analytical difficulty is that CEA does not solve the practical problem of how to allocate money to TB control in combination with other interventions, or even how to combine different approaches to TB control (Tan-Torres Edejer and others 2004). Interpreted literally, CEA says that the best return on total investment is obtained by ranking interventions according to CER and then fully implementing each intervention, from smallest to largest CER, allowing for diminishing returns, until the total budget is spent. This method is unlikely to lead to a balanced health care portfolio in the poorest countries. Besides, the evidence is rarely available to carry out such a complete analysis. The results of CEA are therefore typically used more informally, along with other evidence and constraints, when a mix of health interventions is chosen.

Although this problem will recur in discussions about allocating health budgets, the case for large-scale programs of TB treatment has now been accepted in many parts of the world. That is the fruit of more than 10 years' work on burden, cost, efficacy, effectiveness, and cost-effectiveness. The governments of the less poor members of the group of 22 high-burden countries have demonstrated that they can budget for, and provide, most of the funds needed to reach target levels of case detection and cure (WHO 2004c, 2005). Some of the poorer countries among the 22 are now receiving sufficient external assistance to fill the gaps in their budgets for TB control, principally from the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Consequently, the total reported budget deficit for the high-burden countries in 2005 was remarkably small—just US$119 million—and concentrated in the poorest countries (WHO 2005).

From those findings and observations arise two key questions for global TB control: If the estimated budget gap is filled, would the money be enough to ensure that enhanced DOTS programs reach 70 percent case detection and 85 percent cure—and by when? And if those targets are reached, will the effort be sufficient to achieve the MDG objectives of halving prevalence and death rates by 2015?

As yet, there are only partial answers. On the costs, it is clear that, by moving treatment out of hospitals and into the community, DOTS can often be made cheaper and more convenient for patients and health services without compromising treatment outcome. However, planning for TB control in the poorest countries is still inadequate, and budgets commonly understate the real costs of scaling up national TB control programs (WHO 2004c, 2005). Despite those weaknesses in the budgeting and funding process, the overall expenditure on TB control in high-burden countries has increased since 2000, and the injection of extra effort and money has led to a small acceleration in case finding globally. As a result, case detection under DOTS could reach 50 to 60 percent by 2005, and treatment success should be close to the target level of 85 percent.

A case-detection rate of 50 to 60 percent may not be enough. The analysis in this chapter suggests that the MDG objective of halving the death rate can be reached with 70 percent case detection globally, provided this case detection also generates a 5 to 6 percent annual reduction in the incidence rate between 2003 and 2015. The DOTS program in Peru generated a 6 to 7 percent annual reduction in the incidence rate of pulmonary TB, but that result has not yet been repeated in other high-burden countries with good control programs (for example, India, Morocco, and Vietnam). It is unlikely to be achieved in African countries that currently have high rates of HIV infection.

Although others have emphasized that the costs of infectious disease control can be related to the benefits in complex ways (Brandeau, Zaric, and Richter 2003), we advocate the use of a powerful new method of carrying out CEA, which is based on the observation that mathematical models can be used to generate simple (albeit approximate) and general formulas that relate reward to effort in the management of both epidemic (based on R_0) and endemic (based on dynamics in the vicinity of equilibrium) TB. The results are similar to those obtained by using more complex simulations in specific settings, and they are accurate enough to offer a choice between interventions (Currie and others, 2005). The generality of the method exposes more clearly the reasons some interventions are comparatively cost-effective and indicates the range of conditions under which specific cost-effectiveness results apply. The scope for using this approach for other infectious diseases remains to be explored, but it should be readily applicable in the evaluation of new approaches to TB control, whether through vaccination, drug treatment, the reduction of environmental risks, or improved service delivery.

ACKNOWLEDGMENTS

The authors wish to thank Uli Fruth, Kreena Govender, Ulla Griffiths, Mehran Hosseini, Anne Mills, Mark Perkins, Catherine Watt, Diana Weil, and Brian Williams for help of various kinds during the preparation of this chapter.

REFERENCES

Aaron, L., D. Saadoun, I. Calatroni, O. Launay, N. Memain, V. Vincent, and others. 2004. "Tuberculosis in HIV-Infected Patients: A Comprehensive Review." *Clinical Microbiology and Infection* 10: 388–98.

Adatu, F., R. Odeke, M. Mugenyi, G. Gargioni, E. McCray, E. Schneider, and D. Maher. 2003. "Implementation of the DOTS Strategy for Tuberculosis Control in Rural Kiboga District, Uganda, Offering Patients the Option of Treatment Supervision in the Community, 1998–1999." *International Journal of Tuberculosis and Lung Disease* 7: S63–71.

Albert, H., A. Heydenrych, R. Brookes, R. J. Mole, B. Harley, E. Subotsky, and others. 2002. "Performance of a Rapid Phage-Based Test, FASTPlaqueTBTM, to Diagnose Pulmonary Tuberculosis from Sputum Specimens in South Africa." *International Journal of Tuberculosis and Lung Disease* 6 (6): 529–37.

Albert, H., A. Trollip, T. Seaman, and R. J. Mole. 2004. "Simple, Phage-Based (FASTPlaque) Technology to Determine Rifampicin Resistance of *Mycobacterium tuberculosis* Directly from Sputum." *International Journal of Tuberculosis and Lung Disease* 8: 1114–19.

Andersen, P. 2001. "TB Vaccines: Progress and Problems." *Trends in Immunology* 22: 160–68.

Anderson, R. M., and R. M. May. 1991. *Infectious Diseases of Humans: Dynamics and Control*. Oxford, U.K.: Oxford University Press.

Andries, K., P. Verhasselt, J. Guillemont, H. W. Gohlmann, J. M. Neefs, H. Winkler, and others. 2004. "A Diarylquinoline Drug Active on the ATP Synthase of Mycobacterium Tuberculosis." *Science* 307: 223–27.

Asamoah-Odei, E., J. M. Garcia Calleja, and J. T. Boerma. 2004. "HIV Prevalence and Trends in Sub-Saharan Africa: No Decline and Large Subregional Differences." *Lancet* 364: 35–40.

Behr, M. A, S. A. Warren, H. Salamon, P. C. Hopewell, A. Ponce de Leon, C. L. Daley, and P. M. Small. 1999. "Transmission of *Mycobacterium tuberculosis* from Patients Smear-Negative for Acid-Fast Bacilli." *Lancet* 353: 444–49.

Borgdorff, M. W., N. J. Nagelkerke, C. Dye, and P. Nunn. 2000. "Gender and Tuberculosis: A Comparison of Prevalence Surveys with Notification Data to Explore Sex Differences in Case Detection." *International Journal of Tuberculosis and Lung Disease* 4: 123–32.

Bourdin Trunz, B., P. E. M. Fine, and C. Dye. Forthcoming. Global Impact of BCG Vaccination on Childhood Tuberculous Meningitis and Miliary Tuberculosis.

Brandeau, M. L., G. S. Zaric, and A. Richter. 2003. "Resource Allocation for Control of Infectious Diseases in Multiple Independent Populations: Beyond Cost-Effectiveness Analysis." *Journal of Health Economics* 22: 575–98.

Bucher, H. C., L. E. Griffith, G. H. Guyatt, P. Sudre, M. Naef, P. Sendi, and M. Battegay. 1999. "Isoniazid Prophylaxis for Tuberculosis in HIV Infection: A Meta-Analysis of Randomized Controlled Trials." *AIDS* 13: 501–7.

China Tuberculosis Control Collaboration. 2004. "The Effect of Tuberculosis Control in China." *Lancet* 364: 417–22.

Claessens, N. J. M., F. F. Gausi, S. Meijnen, M. M. Weismuller, F. M. Salaniponi, and A. D. Harries. 2002. "High Frequency of Tuberculosis in Households of Index TB Patients." *International Journal of Tuberculosis and Lung Disease* 6: 266–69.

Cohn, D. L. 2003. "Treatment of Latent Tuberculosis Infection." *Seminars in Respiratory Infections* 18: 249–62.

Cohn, D. L., and W. M. El-Sadr. 2000. "Treatment of Latent Tuberculosis Infection." In *Tuberculosis: A Comprehensive International Approach*, ed. L. B. Reichman and E. S. Hershfield, 471–502. New York: Marcel Dekker.

Comstock, G. W. 2000. "How Much Isoniazid Is Needed for Prevention of Tuberculosis among Immunocompetent Adults? In Reply." *International Journal of Tuberculosis and Lung Disease* 4: 485–86.

Comstock, G. W., C. Baum, and D. E. Snider. 1979. "Isoniazid Prophylaxis among Alaskan Eskimos: A Final Report of the Bethel Isoniazid Studies." *American Review of Respiratory Disease* 119: 827–30.

Comstock, G. W., V. T. Livesay, and S. F. Woolpert. 1974. "The Prognosis of a Positive Tuberculin Reaction in Childhood and Adolescence." *American Journal of Epidemiology* 99: 131–38.

Corbett, E. L., S. Charalambous, V. M. Moloi, K. Fielding, A. D. Grant, C. Dye, and others. 2004. "Human Immunodeficiency Virus and the Prevalence of Undiagnosed Tuberculosis in African Gold Miners." *American Journal of Respiratory Critical Care Medicine* 170: 673–79.

Corbett, E. L., R. W. Steketee, F. O. ter Kuile, A. S. Latif, A. Kamali, and R. J. Hayes. 2002. "HIV-1/AIDS and the Control of Other Infectious Diseases in Africa." *Lancet* 359: 2177–87.

Corbett E. L., C. J. Watt, N. Walker, D. Maher, B. G. Williams, M. C. Raviglione, and C. Dye. 2003. "The Growing Burden of Tuberculosis: Global Trends and Interactions with the HIV Epidemic." *Archives of Internal Medicine* 163: 1009–21.

Cuhadaroglu, C., M. Erelel, L. Tabak, and Z. Kilicaslan. 2002. "Increased Risk of Tuberculosis in Health Care Workers: A Retrospective Survey at a Teaching Hospital in Istanbul, Turkey." *BioMed Central Infectious Diseases* 2: 14.

Currie, C. S. M., K. Floyd, B. G. Williams, and C. Dye. 2005. "Cost Affordability and Cost-Effectiveness of Strategies to Control Tuberculosis in Countries with High HIV, Prevalence." *BMC Public Health* 5 (1): 130.

de Jonghe, E., C. J. Murray, H. J. Chum, D. S. Nyangulu, A. Salomao, and K. Styblo. 1994. "Cost-Effectiveness of Chemotherapy for Sputum Smear-Positive Pulmonary Tuberculosis in Malawi, Mozambique and Tanzania." *International Journal of Health Planning and Management* 9: 151–81.

de Viedma, D. G., M. Marin, S. Hernangomez, M. Diaz, M. J. R. Serrano, L. Alcala, and E. Bouza. 2002. "Reinfection Plays a Role in a Population Whose Clinical/Epidemiological Characteristics Do Not Favor Reinfection." *Archives of Internal Medicine* 162: 1873–79.

Dholakia, R. 1996. *The Potential Economic Benefits of the DOTS Strategy against TB in India.* Geneva: World Health Organization.

Doherty, T. M., A. Demissie, J. Olobo, D. Wolday, S. Britton, T. Eguale, and others. 2002. "Immune Responses to the *Mycobacterium tuberculosis*–Specific Antigen ESAT-6 Signal Subclinical Infection among Contacts of Tuberculosis Patients." *Journal of Clinical Microbiology* 40 (2): 704–6.

Dudley, L., V. Azevedo, R. Grant, J. H. Schoeman, L. Dikweni, and D. Maher. 2003. "Evaluation of Community Contribution to Tuberculosis Control in Cape Town, South Africa." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S48–55.

Dye, C. 2000. "Tuberculosis 2000–2010: Control, but Not Elimination." *International Journal of Tuberculosis and Lung Disease* 4 (Suppl. 2): S146–52.

Dye, C., and M. A. Espinal. 2001. "Will Tuberculosis Become Resistant to All Antibiotics?" *Proceedings of the Royal Society of London, Series B, Biological Sciences* 268: 45–52.

Dye, C., G. P. Garnett, K. Sleeman, and B. G. Williams. 1998. "Prospects for Worldwide Tuberculosis Control under the WHO DOTS Strategy." *Lancet* 352: 1886–91.

Dye, C., S. Scheele, P. Dolin, V. Pathania, and M. C. Raviglione. 1999. "Global Burden of Tuberculosis: Estimated Incidence, Prevalence, and Mortality by Country." *Journal of the American Medical Association* 282: 677–86.

Dye, C., C. J. Watt, D. M. Bleed, S. M. Hosseini, and M. C. Raviglione. 2005. "The Evolution of Tuberculosis Control, and Prospects for Reducing Incidence, Prevalence and Deaths Globally." *Journal of the American Medical Association* 293: 2767–75.

Dye, C., C. J. Watt, D. M. Bleed, and B. G. Williams. 2003. "What Is the Limit to Case Detection under the DOTS Strategy for Tuberculosis Control?" *Tuberculosis* 83: 35–43.

Dye, C., and B. G. Williams. 2000. "Criteria for the Control of Drug-Resistant Tuberculosis." *Proceedings of the National Academy of Sciences USA* 97: 8180–85.

Dye, C., B. G. Williams, M. A. Espinal, and M. C. Raviglione. 2002. "Erasing the World's Slow Stain: Strategies to Beat Multidrug-Resistant Tuberculosis." *Science* 295: 2042–46.

Dye, C., F. Zhao, S. Scheele, and B. G. Williams. 2000. "Evaluating the Impact of Tuberculosis Control: Number of Deaths Prevented by Short-Course Chemotherapy in China." *International Journal of Epidemiology* 29: 558–64.

Espinal, M. A., A. Laszlo, L. Simonsen, F. Boulahbal, S. J. Kim, A. Reniero, and others. 2001. "Global Trends in Resistance to Antituberculosis Drugs." *New England Journal of Medicine* 344: 1294–1303.

Fine, P. E. M. 2001. "BCG Vaccines and Vaccination." In *Tuberculosis: A Comprehensive International Approach*, ed. L. B. Reichman, and E. S. Hershfield, 503–24. New York: Marcel Dekker.

Floyd, K. 2003. "Costs and Effectiveness: The Impact of Economic Studies on TB Control." *Tuberculosis* (Edinburgh) 83: 187–200.

Floyd, K., J. Skeva, T. Nyirenda, F. Gausi, and F. Salaniponi. 2003. "Cost and Cost-Effectiveness of Increased Community and Primary Care Facility Involvement in Tuberculosis Care in Lilongwe District, Malawi." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S29–37.

Floyd, K., D. Wilkinson, and C. Gilks. 1997. "Comparison of Cost Effectiveness of Directly Observed Treatment (DOT) and Conventionally Delivered Treatment for Tuberculosis: Experience from Rural South Africa." *British Medical Journal* 315 (7): 1407–11.

Fordham von Reyn, C., and J. M. Vuola. 2002. "New Vaccines for the Prevention of Tuberculosis. *Clinical Infectious Diseases* 35: 465–74.

Frieden, T. R., P. I. Fujiwara, R. M. Washko, and M. A. Hamburg. 1995. "Tuberculosis in New York City—Turning the Tide." *New England Journal of Medicine* 333: 229–33.

Frieden, T., T. R. Sterling, S. S. Munsiff, C. J. Watt, and C. Dye. 2003. "Tuberculosis." *Lancet* 362: 887–99.

Friedland, G., S. Abdool Karim, Q. Abdool Karim, U. Lalloo, C. Jack, N. Gandhi, and W. El Sadr. 2004. "Utility of Tuberculosis Directly Observed Therapy Programs as Sites for Access to and Provision of Antiretroviral Therapy in Resource-Limited Countries." *Clinical Infectious Diseases* 38 (Suppl. 5): S421–28.

Fruth, U., and D. Young. 2004. "Prospects for New TB Vaccines: Stop TB Working Group on TB Vaccine Development." *International Journal of Tuberculosis and Lung Disease* 8: 151–55.

Garber, A. M., and C. E. Phelps. 1997. "Economic Foundations of Cost-Effectiveness Analysis." *Journal of Health Economics* 16: 1–31.

Glynn, J. R., M. D. Yates, A. C. Crampin, B. M. Ngwira, F. D. Mwaungulu, G. F. Black, and others. 2004. "DNA Fingerprint Changes in Tuberculosis: Reinfection, Evolution, or Laboratory Error?" *Journal of Infectious Diseases* 190: 1158–66.

Goonetilleke, N. P., H. McShane, C. M. Hannan, R. J. Anderson, R. H. Brookes, and A. V. Hill. 2003. "Enhanced Immunogenicity and Protective Efficacy against *Mycobacterium tuberculosis* of Bacilli Calmette-Guérin Vaccine Using Mucosal Administration and Boosting with a Recombinant Modified Vaccinia Virus Ankara." *Journal of Immunology* 171: 1602–9.

Grange, J. 2003. "Immunophysiology and Immunopathology." In *Clinical Tuberculosis*, 3rd ed., ed. P. D. O. Davies, 88–104. London: Arnold.

Hamid Salim, M. A., E. Declercq, A. Van Deun, and K. A. R. Saki. 2004. "Gender Differences in Tuberculosis: A Prevalence Survey Done in Bangladesh." *International Journal of Tuberculosis and Lung Disease* 8: 952–57.

Hernandez-Garduno, E., V. Cook, D. Kunimoto, R. K. Elwood, W. A. Black, and J. M. FitzGerald. 2004. "Transmission of Tuberculosis from Smear Negative Patients: A Molecular Epidemiology Study." *Thorax* 59: 286–90.

Horwitz, M. A., G. Harth, B. J. Dillon, and S. Maslesa-Galic. 2000. "Recombinant Bacillus Calmette-Guérin (BCG) Vaccines Expressing the *Mycobacterium tuberculosis* 30-kDA Major Secretory Protein Induce Greater Protective Immunity against Tuberculosis Than Conventional BCG Vaccines in a Highly Susceptible Animal Model." *Proceedings of the National Academy of Sciences USA* 97: 13853–58.

Hudelson, P. 1996. "Gender Differentials in Tuberculosis: The Role of Socio-Economic and Cultural Factors." *Tubercle and Lung Disease* 77: 391–400.

Jack, W. 2001. "The Public Economics of Tuberculosis Control." *Health Policy* 57: 79–96.

Jamison, D. T., W. H. Mosley, A. R. Measham, and J. L. Bobadilla. 1993. *Disease Control Priorities in Developing Countries.* New York: Oxford University Press.

Johansen, I. S., B. Lundgren, A. Sosnovskaja, and V. Ø. Thomsen. 2003. "Direct Detection of Multidrug-Resistant *Mycobacterium tuberculosis* in Clinical Specimens in Low- and High-Incidence Countries by Line Probe Assay." *Journal of Clinical Microbiology* 41 (9): 4454–56.

Johnson, J. L., A. Okwera, D. L. Hom, H. Mayanja, C. Mutuluuza Kityo, P. Nsubuga, and others. 2001. "Duration of Efficacy of Treatment of Latent Tuberculosis Infection in HIV-Infected Adults." *AIDS* 15: 2137–47.

Krebs, W. 1930. "Die Fälle von Lungentuberkulose in der aargauischen Heilstätte Barmelweid aus den Jahren 1912–1927." *Beiträge zur Klinik der Tuberkulose* 74: 345–79.

Kristensen, I., P. Aaby, and H. Jensen. 2000. "Routine Vaccinations and Child Survival: Follow Up Study in Guinea-Bissau, West Africa." *British Medical Journal* 321: 1435–38.

Letvin, N. L., B. R. Bloom, and S. L. Hoffman. 2001. "Prospects for Vaccines to Protect against AIDS, Tuberculosis, and Malaria." *Journal of the American Medical Association* 285: 606–11.

Lietman, T., and S. M. Blower. 2000. "Potential Impact of Tuberculosis Vaccines as Epidemic Control Agents." *Clinical Infectious Diseases* 30 (Suppl. 3): S316–22.

Marais B. J., R. P. Gie, H. S. Schaaf, A. C. Hesseling, C. C. Obihara, L. J. Nelson, and others. 2004. "The Clinical Epidemiology of Childhood Pulmonary Tuberculosis: A Critical Review of Literature from the Pre-Chemotherapy Era." *International Journal of Tuberculosis and Lung Disease* 8: 278–85.

Marks, G. B., J. Bai, G. J. Stewart, S. E. Simpson, and E. A. Sullivan. 2001. "Effectiveness of Postmigration Screening in Controlling Tuberculosis among Refugees: A Historical Cohort Study, 1984–1998." *American Journal of Public Health* 91: 1797–99.

McMurray, D. N. 2003. "Recent Progress in the Development and Testing of Vaccines against Human Tuberculosis." *International Journal of Parasitology* 33: 547–54.

Menzies, D., M. J. Dion, B. Rabinovitch, S. Mannix, P. Brassard, and K. Schwartzman. 2004. "Treatment Completion and Costs of a Randomized Trial of Rifampin for 4 Months versus Isoniazid for 9 Months." *American Journal of Respiratory and Critical Care Medicine* 170: 445–49.

Moalosi, G., K. Floyd, J. Phatshwane, T. Moeti, N. Binkin, and T. Kenyon. 2003. "Cost-Effectiveness of Home-Based Care versus Hospital Care for Chronically Ill Tuberculosis Patients, Francistown, Botswana." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S80–85.

Murray, C. J. L., E. de Jonghe, H. J. Chum, D. S. Nyangulu, A. Salomao, and K. Styblo. 1991. "Cost Effectiveness of Chemotherapy for Pulmonary Tuberculosis in Three Sub-Saharan African Countries." *Lancet* 338: 1305–8.

Murray, C. J. L., and J. A. Salomon. 1998. "Modeling the Impact of Global Tuberculosis Control Strategies." *Proceedings of the National Academy of Sciences USA* 95: 13881–86.

Mwinga, A., M. Hosp, P. Godfrey-Faussett, M. Quigley, P. Mwaba, B. N. Mugala, and others. 1998. "Twice Weekly Tuberculosis Preventive Therapy in HIV Infection in Zambia." *AIDS* 12: 2447–57.

Nelson, L. J., and C. D. Wells. 2004. "Global Epidemiology of Childhood Tuberculosis." *International Journal of Tuberculosis and Lung Disease* 8: 636–47.

Neuenschwander, B. E., M. Zwahlen, S. J. Kim, E. G. Lee, and H. L. Rieder. 2002. "Determination of the Prevalence of Infection with *Mycobacterium tuberculosis* among Persons Vaccinated against Bacillus Calmette-Guérin in South Korea." *American Journal of Epidemiology* 155: 654–63.

Noertjojo, K., C. M. Tam, S. L. Chan, J. Tan, and M. Chan-Yeung. 2002. "Contact Examination for Tuberculosis in Hong Kong Is Useful." *International Journal of Tuberculosis and Lung Disease* 6: 19–24.

Nyangulu, D. S., A. D. Harries, C. Kang'ombe, A. E. Yadidi, K. Chokani, T. Cullinan, and others. 1997. "Tuberculosis in a Prison Population in Malawi." *Lancet* 350: 1284–87.

Okello, D., K. Floyd, F. Adatu, R. Odeke, and G. Gargloni. 2003. "Cost and Cost-Effectiveness of Community-Based Care in Rural Uganda." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S72–79.

Pai, M., L. W. Riley, and J. M. Colford Jr. 2004. "Interferon-gamma Assays in the Immunodiagnosis of Tuberculosis: A Systematic Review." *Lancet Infectious Diseases* 4 (12): 761–76.

PRC (People's Republic of China) Ministry of Health. 2000. *Report on Nationwide Random Survey for the Epidemiology of Tuberculosis in 2000.* Beijing: PRC Ministry of Health.

Quigley, M. A., A. Mwinga, M. Hosp, I. Lisse, D. Fuchs, J. D. H. Porter, and P. Godfrey-Faussett. 2001. "Long-Term Effect of Preventive Therapy for Tuberculosis in a Cohort of HIV-Infected Zambian Adults." *AIDS* 15: 215–22.

Radhakrishna, S., T. R. Frieden, and R. Subramani. 2003. "Association of Initial Tuberculin Sensitivity, Age, and Sex with the Incidence of Tuberculosis in South India: A 15-Year Follow-Up." *International Journal of Tuberculosis and Lung Disease* 7: 1083–91.

Reed, S. G., M. R. Alderson, W. Dalemans, Y. Lobet, and Y. A. W. Skeiky. 2003. "Prospects for a Better Vaccine against Tuberculosis." *Tuberculosis* 83: 213–19.

Richardson, M., N. M. Carroll, E. Engelke, G. D. Van Der Spuy, F. Salker, Z. Munch, and others. 2002. "Multiple Mycobacterium Tuberculosis Strains in Early Cultures from Patients in a High-Incidence Community Setting." *Journal of Clinical Microbiology* 40: 2750–54.

Rieder, H. L. 1999. "Epidemiologic Basis of Tuberculosis Control." Paris: International Union against Tuberculosis and Lung Disease.

———. 2003. "BCG Vaccines." In *Clinical Tuberculosis,* 3rd ed., ed. P. D. O. Davies, 337–53. London: Arnold.

Rieder, H. L., D. E. Snider Jr., and G. M. Cauthen. 1990. "Extrapulmonary Tuberculosis in the United States." *American Review of Respiratory Disease* 141: 347–51.

Shafer, R. W., and B. R. Edlin. 1996. "Tuberculosis in Patients Infected with Human Immunodeficiency Virus: Perspective on the Past Decade." *Clinical Infectious Diseases* 22: 683–704.

Shilova, M. V., and C. Dye. 2001. "The Resurgence of Tuberculosis in Russia." *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences* 356: 1069–75.

Sinanovic, E., K. Floyd, L. Dudley, V. Azevedo, R. Grant, and D. Maher. 2003. "Cost and Cost-Effectiveness of Community-Based Care for Tuberculosis in Cape Town, South Africa." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S56–62.

Sonnenberg, P., J. R. Glynn, K. Fielding, J. Murray, P. Godfrey-Faussett, and S. Shearer. 2005. "How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners." *Journal of Infectious Diseases* 191: 150–58.

Styblo, K. 1991. *Epidemiology of Tuberculosis.* 2nd ed. The Hague: Royal Netherlands Tuberculosis Association.

Suarez, P. G., K. Floyd, J. Portocarrero, E. Alarcon, E. Rapiti, G. Ramos, and others. 2002. "Feasibility and Cost-Effectiveness of Standardised Second-Line Drug Treatment for Chronic Tuberculosis Patients: A National Cohort Study in Peru." *Lancet* 359: 1980–89.

Suarez, P. G., C. J. Watt, E. Alarcon, J. Portocarrero, D. Zavala, R. Canales, and others. 2001. "The Dynamics of Tuberculosis in Response to 10 Years of Intensive Control Effort in Peru." *Journal of Infectious Diseases* 184: 473–78.

Sutherland, I. 1968. "The Ten-Year Incidence of Clinical Tuberculosis Following 'Conversion' in 2,550 Individuals Aged 14 to 19 Years." Unpublished progress report of the Tuberculosis Surveillance and Research Unit, KNCV, The Hague, Netherlands.

———. 1976. "Recent Studies in the Epidemiology of Tuberculosis, Based on the Risk of Being Infected with Tubercle Bacilli." *Advances in Tuberculosis Research* 19: 1–63.

Sutherland, I., E. Svandova, and S. Radhakrishna. 1982. "The Development of Clinical Tuberculosis Following Infection with Tubercle Bacilli: 1. A Theoretical Model for the Development of Clinical Tuberculosis Following Infection, Linking from Data on the Risk of Tuberculosis Infection and the Incidence of Clinical Tuberculosis in the Netherlands." *Tubercle* 63: 255–68.

Tan-Torres Edejer, T., R. Baltussen, T. Adam, R. Hutubessy, A. Acharya, D. B. Evans, and C. J. L. Murray, eds. 2004. *WHO Guide to Cost-Effectiveness Analysis*. Geneva: World Health Organization.

Terris-Prestholt, F., and L. Kumaranayake. 2003. "Cost Analysis of the Zambian ProTEST Project: A Package to Reduce the Impact of Tuberculosis and Other HIV-Related Diseases." Unpublished report, London School of Hygiene and Tropical Medicine.

Toman, K. 1979. *Tuberculosis Case-Finding and Chemotherapy. Questions and Answers*. Geneva: World Health Organization.

Uplekar, M., V. Pathania, and M. Raviglione. 2001. "Private Practitioners and Public Health: Weak Links in Tuberculosis Control." *Lancet* 358: 912–16.

van Rie, A., R. Warren, M. Richardson, T. C. Victor, R. P. Gie, D. A. Enarson, and others. 1999. "Exogenous Reinfection as a Cause of Recurrent Tuberculosis after Curative Treatment." *New England Journal of Medicine* 341: 1174–79.

Vassall, A., S. Bagdadi, H. Bashour, H. Zaher, and P. V. Maaren. 2002. "Cost-Effectiveness of Different Treatment Strategies for Tuberculosis in Egypt and Syria." *International Journal of Tuberculosis and Lung Disease* 6: 1083–90.

Verver, S., R. M. Warren, Z. Munch, E. Vynnycky, P. D. van Helden, M. Richardson, and others. 2004. "Transmission of Tuberculosis in a High Incidence Urban Community in South Africa." *International Journal of Epidemiology* 33: 351–57.

Vynnycky, E., and P. E. M. Fine. 1997. "The Natural History of Tuberculosis: The Implications of Age-Dependent Risks of Disease and the Role of Reinfection." *Epidemiology and Infection* 119: 183–201.

———. 2000. "Life Time Risks, Incubation Period, and Serial Interval of Tuberculosis." *American Journal of Epidemiology* 152: 247–63.

Whalen, C. C., J. L. Johnson, A. Okwera, D. L. Hom, R. Huebner, P. Mugyenyi, and others. 1997. "A Trial of Three Regimens to Prevent Tuberculosis in Ugandan Adults Infected with the Human Immunodeficiency Virus." *New England Journal of Medicine* 337: 801–8.

WHO (World Health Organization). 2001. *Vaccine Preventable Diseases: Monitoring System—2001 Global Summary*. Geneva: WHO, Department of Vaccines and Biologicals.

———. 2002a. *An Expanded DOTS Framework for Effective Tuberculosis Control*. Geneva: WHO.

———. 2002b. *The World Health Report: Reducing Risks, Promoting Healthy Life*. Geneva: WHO.

———. 2004a. *Anti-Tuberculosis Drug Resistance in the World*. Report 3. Geneva: WHO.

———. 2004b. *Cost and Cost-Effectiveness of Public-Private Mix DOTS: Evidence from Two Pilot Projects in India*. Geneva: WHO.

———. 2004c. *Global Tuberculosis Control: Surveillance, Planning, Financing*. Geneva: WHO.

———. 2004d. *Public-Private Mix for DOTS: Global Progress*. Geneva: WHO.

———. 2004e. *Respiratory Care in Primary Care Services—A Survey in 9 Countries*. Geneva: WHO.

———. 2004f. *World Health Report 2004: Changing History*. Geneva: WHO.

———. 2005. *Global Tuberculosis Control: Surveillance, Planning, Financing*. Geneva: WHO.

Wilkinson, D., K. Floyd, and C. F. Gilks. 1997. "Costs and Cost-Effectiveness of Alternative Tuberculosis Management Strategies in South Africa—Implications for Policy." *South African Medical Journal* 87 (4): 451–55.

Wilkinson, D., S. B. Squire, and P. Garner. 1998. "Effect of Preventive Treatment for Tuberculosis in Adults Infected with HIV: Systematic Review of Randomised Placebo Controlled Trials." *British Medical Journal* 317: 625–29.

Williams, B. G., and C. Dye. 2003. "Antiretroviral Drugs for Tuberculosis Control in the Era of HIV/AIDS." *Science* 301: 1535–37.

Woods, G. L. 2001. "Molecular Techniques in Mycobacterial Detection." *Archives of Pathology and Laboratory Medicine* 125 (1): 122–26.

Young, D. B., and G. R. Stewart. 2002. "Tuberculosis Vaccines." *British Medical Bulletin* 62: 73–86.