Interventions to reduce tuberculosis mortality and transmission in low- and middle-income countries*

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Abstract Tuberculosis is among the top ten causes of global mortality and affects low-income countries in particular. This paper examines, through a literature review, the impact of tuberculosis control measures on tuberculosis mortality and transmission, and constraints to scaling-up. It also provides estimates of the effectiveness of various interventions using a model proposed by Styblo. It concludes that treatment of smear-positive tuberculosis using the WHO directly observed treatment, short-course (DOTS) strategy has by far the highest impact. While BCG immunization reduces childhood tuberculosis mortality, its impact on tuberculosis transmission is probably minimal. Under specific conditions, an additional impact on mortality and transmission can be expected through treatment of smear-negative cases, intensification of case-finding for smear-positive tuberculosis, and preventive therapy among individuals with dual tuberculosis–HIV infection. Of these interventions, DOTS is the most cost-effective at around US$ 5–40 per disability-adjusted life year (DALY) gained. The cost for BCG immunization is likely to be under US$ 50 per DALY gained. Treatment of smear-negative patients has a cost per DALY gained of up to US$ 100 in low-income countries, and up to US$ 400 in middle-income settings. Other interventions, such as preventive therapy for HIV-positive individuals, appear to be less cost-effective. The major constraint to scaling up DOTS is lack of political commitment, resulting in shortages of funding and human resources for tuberculosis control. However, in recent years there have been encouraging signs of increasing political commitment. Other constraints are related to involvement of the private sector, health sector reform, management capacity of tuberculosis programmes, treatment delivery, and drug supply. Global tuberculosis control could benefit strongly from technical innovation, including the development of a vaccine giving good protection against smear-positive pulmonary tuberculosis in adults; simpler and shorter drug regimens for treatment of tuberculosis disease and infection; and improved diagnostics for tuberculosis infection and disease.

Keywords Tuberculosis, Pulmonary/drug therapy/mortality/transmission; BCG vaccine/economics; Cost-benefit analysis; Cost of illness; Review literature; United Republic of Tanzania; Viet Nam (*source: MeSH, NLM*).

Mots clés Tuberculose pulmonaire/chimiothérapie/mortalité/transmission; Vaccin BCG/économie; Analyse coût bénéfice; Coût maladie; Revue de la littérature; République-Unie de Tanzanie; Viet Nam (*source: MeSH, INSERM*).

Palabras clave Tuberculosis pulmonar/quimioterapia/mortalidad/transmisión; Vacuna BCG/economía; Análisis de costo-beneficio; Costo de la enfermedad; Literatura de revisión; República Unida de Tanzanía; Viet Nam (*fuente: DeCS, BIREME*).

Bulletin of the World Health Organization 2002;80:217-227.

Voir page 224 le résumé en français. En la página 224 figura un resumen en español.

Introduction

Tuberculosis is among the top ten causes of global mortality (*1*, *2*). It has been estimated that approximately one-third of the world's population is infected with the tuberculosis bacillus, and that each year 8 million people develop tuberculosis disease and 1.8 million die of the disease (*3*, *4*). Approximately 80% of tuberculosis cases are found in 23 countries; the highest incidence rates are found in Africa and South-East Asia (*3*, *4*). The tuberculosis situation has worsened over the past two decades in Africa owing to the HIV/AIDS epidemic, and in Eastern Europe in association with multidrug resistance, following deterioration of the health infrastructure (*4*, *5*).

Tuberculosis is caused by *Mycobacterium tuberculosis*, a microorganism whose principal reservoir is humans. *M. tuberculosis* is spread by patients with pulmonary tuberculosis, especially those with positive sputum smears (*6–11*). Of those becoming infected, 10–12% will develop tuberculosis disease after a period ranging from weeks to decades (*8*, *12*, *13*). The risk of disease declines steeply with time after infection. Disease may also occur after reinfection (*7*, *12*, *14*).

In 2000, the G8 group of countries called for the scaling-up of interventions against HIV, tuberculosis and malaria, and set a target for the reduction in tuberculosis mortality of 50% by 2010 (*15*). This target may be difficult to achieve (*16*) despite

* Based on: Borgdorff MW, Floyd K, Broekmans JF. *Interventions to reduce tuberculosis mortality and transmission in low- and middle-income countries: effectiveness, cost-effectiveness, and constraints to scaling up.* (CMH Working Paper Series, Paper No. WG5: 8. Available at: URL: www.cmhealth.org/wg5_paper8.pdf).

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Ref. No. **01-1533**

the availability of the World Health Organization (WHO) directly observed treatment, short-course (DOTS) strategy for the treatment of tuberculosis, which is considered to be a very cost-effective health intervention with a large potential impact (*17–20*). Reasons are the slow epidemiology of tuberculosis and the slowness with which the DOTS strategy is being adopted (*18*, *21–24*).

After describing available tuberculosis interventions, we assess their effectiveness at the individual and population level, and the extent to which an additional impact can be expected from an expansion in tuberculosis control measures. This assessment is based mainly on a literature review. In addition, we provide cost-effectiveness estimates for different interventions using an extension of a model proposed by Styblo (*25*, *26*), and explore constraints to the scaling-up of interventions. This paper is restricted to drug-susceptible tuberculosis. In countries where multidrug resistance is common, special measures are needed, which are discussed elsewhere (*27*). In settings with a high prevalence of HIV infection, HIV prevention will be of major importance for tuberculosis control. For a discussion of the effectiveness of these HIV prevention measures we refer to other reviews (e.g. *28*). Among tuberculosis patients with HIV, the risk of death is very high (*29*). Most of the deaths are attributed to HIV. While the present paper addresses tuberculosis treatment, it does not deal with measures such as antiretroviral treatment to reduce HIV-associated mortality.

Available tuberculosis interventions

Diagnosis and treatment of smear-positive tuberculosis

The main components of the WHO DOTS strategy are political commitment, case detection among self-reporting patients with symptoms using sputum smear microscopy, short-course chemotherapy under proper management, including directly observed therapy, assurance of a regular drug supply, and a strong surveillance and monitoring system (*4*, *30*). The need for directly observed treatment as a universal requirement is controversial, since the success of some tuberculosis control programmes is attributed to other programme elements (*31–35*). The importance given to monitoring treatment outcomes is non-controversial. The DOTS strategy aims at detecting at least 70% of new smear-positive cases and successfully treating 85% of them (*4*).

BCG immunization

Unfortunately, the protective efficacy of BCG, the most widely used vaccine against pulmonary tuberculosis, varies from 0% to 80% (*36–40*). Explanations for this variability include differences in the prevalence of infection with environmental mycobacteria (*37*, *39*, *40*) and differences between BCG strains (*38*). BCG gives good protection (75–80%) against disseminated tuberculosis, including tuberculous meningitis, in childhood (*37*). However, the impact of BCG on tuberculosis transmission is probably minimal. BCG is given at birth or as soon as possible thereafter, and although the duration of protection is uncertain, it may not be longer than 15 years, thus limiting protection against infectious pulmonary tuberculosis, which occurs mainly in adults (*37*, *41*).

Diagnosis and treatment of smear-negative tuberculosis

Most tuberculosis control programmes provide treatment to smear-negative patients. Unfortunately, the diagnosis of smear-negative tuberculosis is difficult. Chest X-rays are an important tool, but their interpretation has limited specificity and inter-reader repeatability (*42*). Moreover, patients with HIV infection may have a normal chest X-ray despite active tuberculosis (*43*, *44*). Mycobacterial cultures would be helpful, but are not widely available in high-burden countries. Thus, programmes often employ diagnostic algorithms, which require that tuberculosis suspects with a negative smear are first treated with antibiotics which are ineffective against tuberculosis. Only after this treatment has failed (or in critically ill patients) is tuberculosis treatment started (*45*).

Active case-finding and treatment of smear-positive tuberculosis

Although active case-finding has made only a limited contribution to reducing tuberculosis transmission in Europe (*46–48*), mathematical models have suggested that it may have substantial benefits in high-prevalence countries (*21*, *22*). The DOTS strategy focuses on patients who report to health services themselves because of symptoms, while active (or intensified) case-finding involves a special effort by the health service to detect cases, either in the general population, or in special risk groups such as prisoners or people in hyperendemic neighbourhoods.

Population surveys using mass miniature radiography may detect approximately 90% of prevalent tuberculosis cases participating in the survey. However, their cost is high. Population surveys using tuberculosis symptoms to screen patients are less costly to implement, but may detect only 70% of cases (*49*), depending on the target groups and the methods used to elicit symptoms (*50*). Intensified case-finding among outpatients with respiratory symptoms worked well during one study (*51*), but routine application of a chronic cough register had disappointing results (*52*).

Preventive therapy in people with HIV infection

HIV-infected people who are also infected by *M. tuberculosis* are at a strongly increased risk of developing active tuberculosis, depending on the extent of their immunodeficiency (*5*, *53–55*). Smear-positive tuberculosis cases with HIV coinfection may be slightly less infectious than those with no HIV infection but the difference is probably not large (*56–58*). Primary prevention of HIV infection is therefore of major importance for tuberculosis control. The effectiveness of various HIV prevention measures is reviewed elsewhere (e.g. *28*).

The risk of active tuberculosis among individuals with dual tuberculosis and HIV infection can be reduced by treatment for 6–12 months with isoniazid or for 2 months with rifampicin and pyrazinamide (*59–64*). This treatment can also be administered to prevent recurrence in HIV-infected tuberculosis patients who have completed tuberculosis therapy (*65*). Protective efficacy is 60–80% in the short term (*59*, *60*). However, the duration of protection may be shorter in HIV-infected than in non-HIV-infected individuals, depending on whether elimination of infection can be achieved and on the risk of reinfection. Loss of patients to the programme at every

step from identification of those eligible to completion of therapy is a major concern (*66*, *67*).

Antiretroviral therapy slows the development of immunodeficiency in HIV-infected persons, may restore immunocompetence, and delays the onset of tuberculosis (*68*, *69*). However, it is unclear whether this treatment reduces the lifetime risk of tuberculosis in such individuals or whether specific antituberculosis preventive therapy is required.

Preventive therapy for contacts of tuberculosis patients, and adults in the general population

Contact investigations to identify recent infection tend to be limited to children within the household, restricting coverage of this intervention. Preventive therapy with isoniazid reduces the risk of disease among recently infected children by 60–80%, and side-effects are rare (*70*). Preventive treatment among adults with latent tuberculosis infection also has a protective efficacy in the range 60–80%, depending on the duration of therapy (*70*, *71*). Effectiveness in routine practice may be limited by partial uptake and compliance.

Effectiveness of interventions

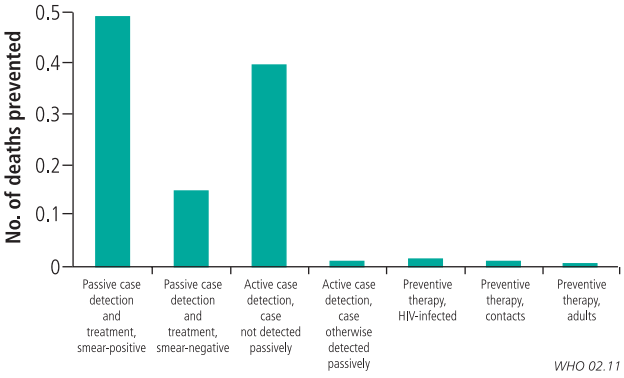
Mortality reduction in persons undergoing treatment

An overview of the reduction in mortality resulting from various interventions is presented in Fig. 1. Without treatment, 60–70% of smear-positive patients without HIV coinfection would die within a few years (*72*), while their case fatality ratio under the DOTS strategy would be approximately 5% (*26*). In smear-negative cases, the case fatality ratio would be approximately 20% without treatment (*8*) and less than 5% with treatment. Case fatality ratios in HIV-infected tuberculosis patients are much higher, but deaths are attributed to HIV.

The direct health impact of active case-finding is probably substantial for patients who would otherwise not have been detected, but precise estimates are not available. In patients who would otherwise have been detected through self-reporting, the additional impact of active case-finding on mortality is limited, since treatment outcome is generally favourable in self-reporting patients (*73*). In settings where treatment results among self-reporting patients are not so favourable, results among actively detected cases are unlikely to be any better.

The impact of preventive therapy on mortality can only be estimated very crudely. We assume that preventive therapy will only be considered by programmes with high rates of case detection and cure of smear-positive tuberculosis, and that, for each tuberculosis case prevented, 0.1 death is prevented. Preventive therapy in HIV-infected persons only affects HIV-associated mortality. In children without HIV infection who are contacts of tuberculosis patients, if the lifetime risk of developing tuberculosis is 12%, preventive therapy with a protective efficacy of 60% would prevent 0.07 tuberculosis cases and 0.007 tuberculosis deaths. In adults without HIV infection who have latent tuberculosis infection, if the average lifetime risk of developing tuberculosis is 5%, preventive therapy would prevent 0.03 tuberculosis cases and 0.003 tuberculosis deaths. However, additional deaths due to side-effects of the drugs reduce these benefits. Disease risks and thus benefits of preventive therapy are larger in those with HIV infection.

Fig. 1. **Number of deaths avoided when treating a single case compared with no treatment**



Reducing first-generation infectious cases

An overview of the estimated impact of control measures on tuberculosis transmission is shown in Fig. 2. To estimate the impact of DOTS on transmission we followed the reasoning of Styblo (*25*, *26*). Styblo assumed that in the absence of treatment each smear-positive case would be infectious for 2 years and thus generate 2ß infections (where ß is the number of infections generated per case per year). Each new self-reporting case detected after, on average, 4 months would have infected 0.33ß contacts. With a relapse rate of 15% and a 4-month delay among relapsed cases, another 0.05ß infections are generated. A failure rate of 5%, each failure case remaining infectious for 3 years, would add another 0.15ß infections per new case. A good DOTS programme could therefore reduce the number of infections per case from 2ß to 0.53ß, i.e. by 73%. If, without DOTS, each infectious case would generate on average one other first-generation infectious case, treatment of each case under the DOTS programme would prevent 0.73 new infectious cases.

The number of infections generated by a smear-negative pulmonary tuberculosis case is approximately 10–20% of that generated by a smear-positive case (*9*–*11*). DOTS would therefore prevent 0.1 future cases among smear-negative cases.

For patients detected through active case-finding, it is estimated that the infectious period could be reduced by 50%. Patients who would otherwise have been found through self-reporting would therefore generate 0.37ß infections rather than 0.53ß infections, a reduction of 0.16ß infections and 0.08 infectious cases. Patients who would otherwise not report to the health services with symptoms would generate 1.2ß infections (1ß at detection and 0.2ß assuming similar failure and relapse rates as among self-reporting patients) rather than 2ß infections without active case-finding, preventing 0.4 future infectious cases.

The impact of preventive therapy on transmission lies in the direct prevention of infectious tuberculosis cases. If the lifetime risk of developing tuberculosis among those with tuberculosis-HIV coinfection is estimated at 25%, and preventive therapy would give a lifetime protection of 25% (*63*), 0.06 infectious cases would be prevented per person treated. If children who are contacts of tuberculosis cases have a lifetime risk of developing infectious tuberculosis of 5%, preventive therapy with a protective efficacy of 60% would prevent 0.03 infectious cases per child treated. Among adults in

Fig. 2. **Number of future infectious cases avoided directly when treating a single case compared with no treatment.** For treatment of smear-negative tuberculosis the number of future cases avoided is estimated assuming that each smear-positive case would generate one smear-positive case in the absence of treatment. For preventive therapy, the infectious cases avoided directly would have occurred in those receiving the treatment

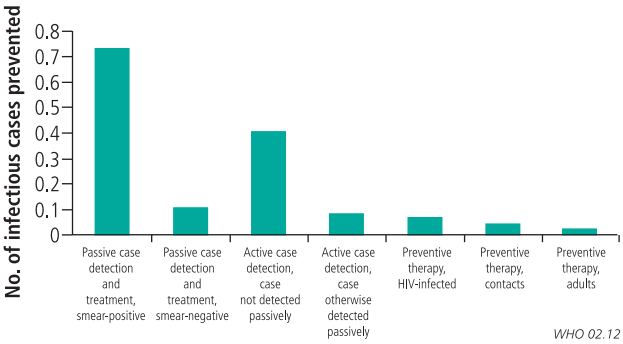
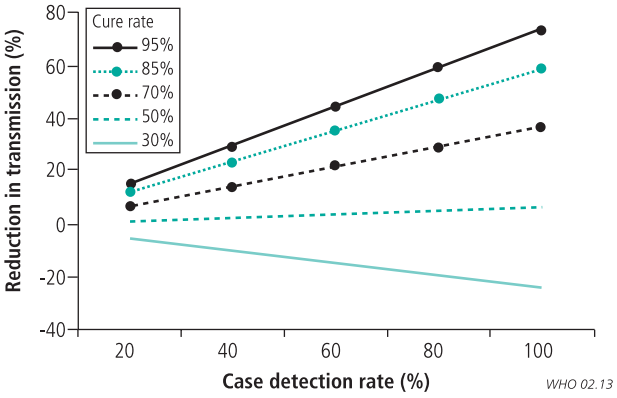


Fig. 3. **Reduction of tuberculosis transmission as a result of treatment of patients self-reporting to health facilities under various programme conditions**



the general population with latent infection, the lifetime risk of developing infectious tuberculosis due to reactivation may be in the order of 2.5%. Preventive therapy would prevent approximately 0.015 infectious cases per person treated.

Short-term impact of case-finding and treatment on transmission

The impact of DOTS on transmission depends on case detection and cure rates. The reduction in transmission in a given population, estimated using the same assumptions as above under varying case detection and cure rates, is shown in Fig. 3. The cure rate is simplified here as 1-failure rate. Deaths are not considered to be programme failures in this analysis, since there is no further contribution to transmission. The analysis shows that, for a programme with a cure rate of less than 50%, tuberculosis transmission would increase. Since such a programme would reduce the case fatality ratio without curing enough patients, the prevalence of infectious cases would increase.

The additional impact of active case-finding will depend on the frequency of screening and the sensitivity of the screening method. For instance, if screening was undertaken once in 2 years, only one-sixth of patients otherwise detected through self-reporting would have a chance of being detected actively (as the average delay period is assumed to be 4 months). Fig. 4 illustrates, for a range of case detection and cure rates, the additional reduction in transmission that would be achieved with active case-finding at various levels of frequency and sensitivity. This analysis shows that active case-finding offers little benefit when cure rates are below 70%. As might be expected, the largest benefit is observed when case detection rates are low. Active case-finding may be particularly efficient in tuberculosis risk groups, depending on their size and level of risk.

Country examples: United Republic of Tanzania and Viet Nam

The potential contribution of tuberculosis intervention measures depends on the epidemiological situation in countries and the current implementation of control. The United Republic of Tanzania and Viet Nam are among the 23 high-burden countries in which 80% of the world's tuberculosis cases are found, and both have well-established DOTS programmes (*24*). The contribution of various tuberculosis control measures in these two countries is summarized in Table 1. In our analysis, published figures were used as far as possible (*3*). The numbers of deaths and cases prevented per 100 000 population in the short term by the current programmes are comparable. The United Republic of Tanzania has a higher incidence of tuberculosis, but lower case detection and cure rates; the greatest additional impact on mortality and transmission would result from intensifying case-finding and preventive therapy in patients with tuberculosis–HIV coinfection. In Viet Nam, the greatest impact would result from treating a larger number of smear-negative tuberculosis cases and intensifying case-finding.

Limitations of the effectiveness estimates

The parameters used to estimate the effectiveness of different interventions are uncertain, in particular those related to reducing transmission. For instance, the duration of the infectious period and the degree of infectiousness over this period are not well known and perhaps impossible to measure directly. Although the simple model we used has the advantage that it highlights the role of a few key determinants, it may have the disadvantage of ignoring potentially important variations (e.g. in diagnostic delay) and associations (e.g. between diagnostic delay and the case detection rate). A limitation of our approach to the comparison of numbers of infectious cases prevented directly is that this effect occurs at different points in time for the different interventions. Ignoring the time factor probably results in an underestimate of the effectiveness of preventive therapy in people with tuberculosis–HIV coinfection and an overestimate in individuals without HIV infection in comparison with the effectiveness of case-finding and treatment. Moreover, the simple model gives limited insight into long-term impact. To overcome this limitation, a dynamic transmission model may be needed (e.g. *12*, *13*, *17*, *21*, *22*, *74*). However, dynamic transmission models remain subject to the other uncertainties mentioned above.

Fortunately, many uncertainties influence these effectiveness estimates in a similar way, with little consequence for relative effectiveness. Moreover, since the estimates suggest large differences in effectiveness between DOTS and the other intervention options, conclusions on the relative strength of DOTS are unlikely to be greatly affected. However, it is clear

Fig. 4. **Additional reduction of tuberculosis transmission due to active case-finding under various programme conditions for patients self-reporting to health facilities.** A. Sensitivity 90%, frequency once in 5 years. B. Sensitivity 70%, frequency once in 2 years. C. Sensitivity 50 %, frequency annual

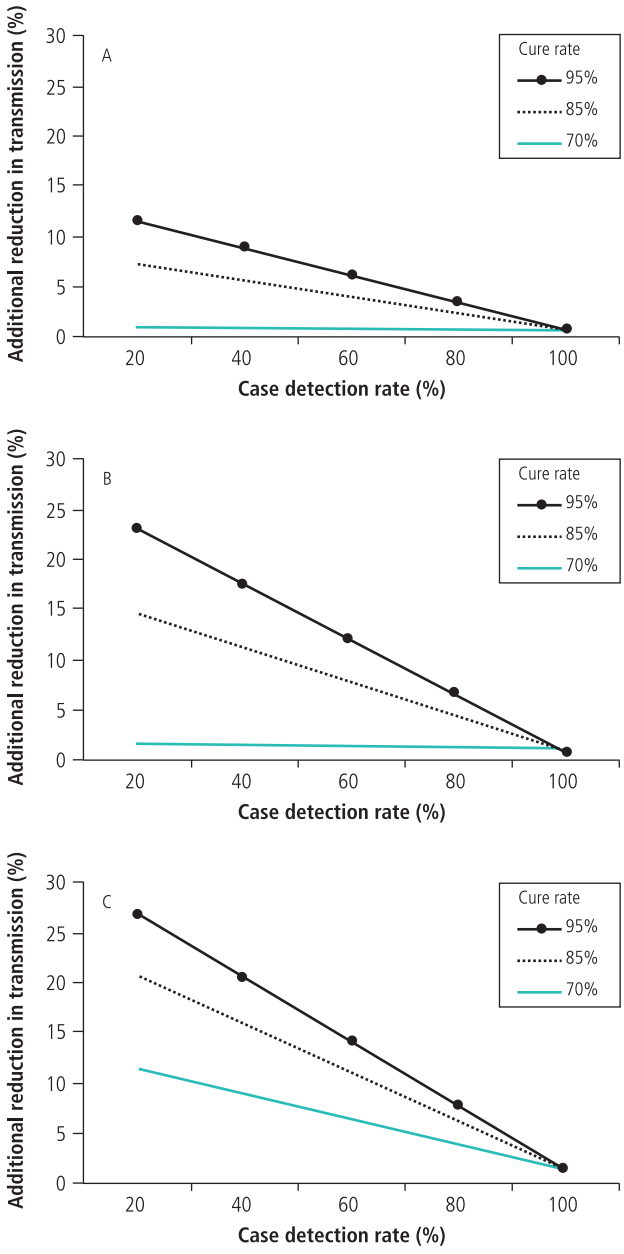


Table 1. **Expected impact of various tuberculosis control measures on mortality and transmission in United Republic of Tanzania and Viet Nam[a]**

Strategy	Total no. of tuberculosis deaths prevented directly per 100 000 population per year		Total no. of infectious cases prevented directly per 100 000 population 1 per year	
	United Republic of Tanzania	Viet Nam	United Republic of Tanzania	Viet Nam
Current programme				
Treatment of smear-positive, self-reporting patients	35.0	34.9	46.1	50.9
Treatment smear-negative self-reporting patients	7.7	3.2	5.1	2.3
Total	**42.6**	**38.0**	**51.2**	**53.2**
Additional options				
Allow more smear-negative cases on treatment programme	2.7	8.0	1.8	5.3
Active case-finding				
Screening yearly, sensitivity of screening method 50%	6.9	3.3	13.8	6.6
Preventive therapy				
HIV–tuberculosis cases	3.6	0.3	7.2	0.5
Contacts (children)	0.2	0.2	1.6	1.6
Adults, general population	0.2	0.3	3.6	6.5

[a] Assumptions
United Republic of Tanzania: incidence 127/100 000, case detection rate 55%, failure rate (including defaulters) 10%, infection prevalence among adults 40% for tuberculosis and 8% for HIV.
Viet Nam: incidence 85/100 000, case detection rate 82%, failure rate 5%, infection prevalence among adults 60% for tuberculosis and <0.5% for HIV.
Both countries: achievable coverage for active case-finding for adult population 80%, for HIV-infected cases 5%, for contacts 50%, and for adults with latent infection 80%; 3 child household contacts per infectious case; treatment completion of preventive therapy 60% among HIV-infected persons and 50% among contacts and adults in general population; risk of progression from infection to infectious disease 25% among HIV-infected persons, 5% among contacts, and 1.5% among adults in general population; benefits of a single round of preventive therapy to adults spread out over 20 years, effectiveness estimates as in Fig. 1–4.

that the estimated impact of the interventions provides a rough guide only, and further studies to improve estimates are needed.

Cost-effectiveness estimates

There have been few studies of the cost-effectiveness of tuberculosis control interventions in low- and middle-income countries (Table 2). Most studies have focused on DOTS for new smear-positive cases (*75–83*), with only one study each for BCG (*84*), preventive therapy (*62*) and active case-finding (*22*), and two unpublished studies of DOTS for smear-negative patients (*83*). There are no published studies on preventive therapy in contacts or those with latent infection.

The best-known results are probably those from the study undertaken in Malawi, Mozambique and the United Republic of Tanzania (*75*, *76*). This indicated that DOTS for new smear-positive patients cost US$ 1–3 per year of life gained (US$ 1–4 at 2000 prices), and was the basis for the World Bank 1993 estimate that tuberculosis treatment cost US$ 1–3 per DALY gained (*17*). However, these figures may be underestimates in some settings. Costs are likely to be relatively low in this case because the countries studied are some of the poorest in the world. Moreover, the effects achieved may be smaller elsewhere; the results were based on an average gain of 24 years of life per death averted (*76*) — now considered too high in countries seriously affected by HIV — and on some of the best treatment outcomes achieved to date. Many countries have poorer cure rates and higher case fatality ratios (*4*). Higher costs per DALY gained in middle-income countries are supported by studies from South Africa (*81–83*), which report a cost per patient

Table 2. **Summary of cost-effectiveness studies of tuberculosis interventions.** While the DOTS strategy is not usually explicitly identified as being one of the evaluated approaches to treatment, the chemotherapy strategies considered generally conform to the main principles of DOTS

Place, date of study	Main methods	Key results and conclusions	Reference
DOTS, new smear-positive cases			
Malawi, Mozambique, United Republic of Tanzania, 1991	Analysis of cost data from 1988–89 and empirical treatment outcome data from 1980s; epidemiological model used to assess secondary deaths averted through prevented transmission.	Cost per DALY gained US$ 1–3 for short-course chemotherapy. Cost per patient treated (converted to 2000 prices), US$ 101–129 for ambulatory care and US$ 226–306 for treatment involving 2-month hospital stay at treatment outset. Short-course treatment more cost-effective than standard course.	*75*, *76*
Botswana, 1986; Thailand, 1992; Indonesia, 1989	Analysis of empirical cost and effectiveness data.	Short-course chemotherapy more cost-effective than standard course.	*77*, *78*, *79*
Uganda, 1995	Analysis of empirical cost and effectiveness data for existing care strategy (hospitalization in intensive phase); assumptions about effectiveness for ambulatory care.	Ambulatory care with strengthened supervision likely to be more cost-effective than hospital-based care.	*80*
South Africa, 1997	Analysis of empirical cost and treatment outcome data.	Community-based care more cost-effective than 3 other health-facility-based approaches to care, including one widely used in rural Africa (2-month hospital stay at treatment outset). Cost per patient (converted to 2000 prices) US$ 760 for community-based care, US$ 2078 for treatment with 2-month hospital stay.	*81*, *82*
Botswana, Kenya, Malawi, South Africa, Uganda, 1997–2000,	Analysis of empirical cost and treatment outcome data for conventional health facility-based approaches to care and increased decentralization, and involvement of communities in provision of care; estimation of cost per DALY gained, based on similar assumptions to those used in first study listed above but with appropriate adjustments for high rates of HIV infection among tuberculosis patients (from 40% in South Africa to 80% in Malawi), and the effect of this on deaths averted per patient treated and DALYs gained per death averted.	Pilot approaches involving decentralization and community-based care almost always more cost-effective than conventional health-facility-based care. Cost per DALY gained (converted to 2000 prices) estimated as US$ 2–15 in low-income countries and US$ 10–16 in South Africa, depending on the treatment strategy.	*83*
DOTS, new smear-negative cases			
Malawi and Kenya as part of WHO-coordinated ''Community Care for TB in Africa'' project (listed as seventh study. above	Analysis of empirical cost and treatment outcome data collected 1997–99. Estimation of cost per DALY gained made, based on similar assumptions to those used in first study listed above but with appropriate adjustments for lower infectiousness of cases, higher rates of false-positive diagnosis, and high rates of HIV infection (80% in Malawi and 40% in Kenya) on deaths averted per patient treated and DALYs gained per death averted.	Cost-effectiveness of treatment for smear-negative cases in Kenya estimated as US$ 13–62 per DALY gained, and as US$ 15–16 in Malawi, depending on the treatment strategy being used. Cost per DALY gained 1.4–3.5 times poorer than treatment for smear-positive cases in Malawi, and 6–11.6 times poorer in Kenya.	*83*
BCG			
Developing countries, 1990	Estimation of costs and effectiveness based on existing studies, in particular in United Republic of Tanzania, Botswana and Indonesia.	Cost-effectiveness may be similar to that of treatment at high annual rates of infection, poorer at low rates. Cost per death averted US$ 144 at 1986 (US$ 224 at 2000) prices in Botswana when BCG is added to existing immunization programme.	*84*
Active case-finding			
Major geographical regions (as defined by the World Bank), 1998	Estimation of threshold costs at which strategy would have a cost per DALY gained below per capita GNP.	Strategy may be cost-effective in low- and middle-income countries in e.g. Asia, sub-Saharan Africa.	*22*
Preventive therapy in HIV-positive adults			
Uganda, 1999	Analysis of cost data from other studies (*79*); effectiveness modelled using efficacy data from trials (no adjustment for compliance in practice under routine programme conditions); estimation of secondary infections caused per tuberculosis case from elsewhere.	Cost per DALY gained US$ 14–260 (medical costs only).	*62*

around 6–9 times higher than the figures from Malawi, Mozambique and the United Republic of Tanzania. This would suggest a cost per DALY gained of around US$ 10–40 in middle-income countries in the absence of HIV. The most recent study takes into account the influence of HIV on cost-effectiveness by including an analysis of HIV prevalence among tuberculosis patients and the effect of this on average deaths averted and years of life gained per patient treated. The study indicates a cost per DALY gained of US$ 2–15 in low-income African countries, and US$ 10–16 for ambulatory treatment in urban South Africa (*83*).

The finding that the cost-effectiveness of BCG is comparable to that of DOTS for new smear-positive patients in settings where the annual risk of infection is high should be treated with some caution (*84*). It is based on the assumption of 50% vaccine efficacy, which may be too high, and on conservative estimates of the impact of treatment of new smear-positive cases on transmission. Nevertheless, the estimated cost per death averted of US$ 144 at 1986 prices (US$ 224 at 2000 prices) of adding BCG to an existing immunization programme translates into a cost per DALY gained of less than US$ 10. On this basis, even if BCG efficacy is much lower, the cost per DALY gained is unlikely to be above US$ 50.

Where the cost-effectiveness of DOTS for new smear-negative cases has been estimated for the same place and time period as for smear-positive cases (in Kenya and Malawi (*83*)), the cost per DALY gained was 1.4–11.6 times higher for smear-negative cases (with lower costs and lower effectiveness). This implies a cost per DALY gained of US$ 2–100 in low-income settings, and up to US$ 400 in middle-income settings.

It is difficult to draw definitive conclusions regarding the absolute or relative cost-effectiveness of active case-finding and preventive therapy. Further research on costs and effects in practice is required.

Despite the limited evidence, the results indicate that DOTS for new smear-positive cases is the most cost-effective of the available interventions. Where case detection and cure rates are currently below WHO targets, additional resources should initially be used to expand this intervention. On the basis of the current suggested benchmarks (*16*, *22*, *84*, *85*), BCG immunization and DOTS for new smear-negative cases are capable of increasing the effectiveness of tuberculosis control programmes at an acceptable cost. More data are needed to clarify whether the same is true of preventive therapy and active case-finding.

Constraints to scaling-up

WHO estimates that 23% of all smear-positive tuberculosis patients detected in 1999 were diagnosed within a DOTS programme (*4*). Although this represents considerable progress since 1995, when the proportion was 11%, major scaling-up is still required. In 1998, the WHO ad hoc committee on the tuberculosis epidemic identified the following constraints: financial shortages, human resource problems, organizational factors, drug supply problems, and lack of public awareness (*86*). Weak political commitment was considered to be the overriding constraint.

Since 1998, tuberculosis has become more important on the international agenda. In 2000, a conference in Amsterdam involving ministers from 20 of the 23 high-burden countries and international donors endorsed the urgency of tuberculosis control and participants accepted responsibility for tackling the problem (*87*). Also in 2000, as mentioned earlier, the G8 group of countries called for intensification of public health efforts against HIV, malaria, and tuberculosis (*15*).

In countries that have reached the WHO targets of a 70% case detection and an 85% cure rate, the major challenge is financial sustainability (*86*). External financial support has been used to facilitate initial implementation and expansion. Unfortunately, the time-scale for external support (typically 5 years or less) is much shorter than that for tuberculosis control (decades). In countries where DOTS implementation is rapidly expanding, political will at the central level may not be matched at lower (provincial, district) levels of government (*86*). In addition, special efforts may be required to ensure acceptance of the DOTS strategy by health professionals.

In many high-burden countries, private health care providers comprise an important part of the health system. However, case detection and cure rates in the private sector are often unknown. While not-for-profit nongovernmental organizations have contributed successfully to tuberculosis control, the involvement of other private sector providers may be more problematic (*88–90*). The ongoing reform of the health sector in many countries may provide opportunities to give tuberculosis control higher priority as an important public health problem with a cost-effective solution (*91–95*). Unfortunately, in some countries, such reform has led to weakening of tuberculosis control (*96–98*).

Ensuring access to antituberculosis drugs is a key task of tuberculosis control programmes. Central ordering may allow drugs to be obtained at a reduced cost, but may also be associated with bureaucratic delays. To prevent interruption of treatment, "patient-wise" boxes (one box per patient, each containing the full treatment course) have been found to be helpful, for instance in India (*99*). The Global Tuberculosis Drug Facility (a global partnership initiative established in 2001) is expected to facilitate rapid access to low-cost drugs and provision of drugs in emergency situations.

Preventive therapy in individuals with tuberculosis–HIV coinfection may substantially contribute to tuberculosis control in countries with a high prevalence of HIV infection. The major practical problems for this approach lie in identifying the target group and in ensuring compliance with the treatment. Voluntary counselling and testing initiatives (e.g.*100*) will be important in this regard. It is clear that HIV and tuberculosis programmes will need to work together to promote HIV prevention and improve patient care for HIV-infected individuals, including tuberculosis treatment and prevention.

Preventive therapy in child contacts within households is unlikely to have an impact on tuberculosis transmission in most settings, since these individuals usually represent a minority of all contacts. Therefore, scaling up this intervention does not appear to be a priority. Large-scale preventive therapy in the general population is unlikely to be feasible with currently available diagnostics and drugs.

Recent advances in research, including the sequencing of the genome of *M. tuberculosis*, have raised hopes that better vaccines may become available over the next few decades (*101*, *102*). There is clearly a need for a new vaccine with a high protective efficacy against smear-positive tuberculosis in adults. New drugs with shorter and simpler regimens, and improved diagnostics for tuberculosis disease and infection, would also make a substantial contribution to global tuberculosis control.

Our review indicates that the WHO DOTS strategy is by far the most effective tuberculosis control strategy currently available. Expansion of this strategy could have a rapid impact on tuberculosis mortality and prevalence. However, in HIV-affected countries, it is unlikely to reduce tuberculosis incidence by 50% over the next decade, the target set by the G8. HIV prevention and control are therefore of major importance for tuberculosis control. ■

Acknowledgements

Valuable comments on earlier drafts of this paper were made by Chris Dye, Saidi Egwaga, Tom Frieden, Peter Gondrie, Prabhat Jha, Nico Nagelkerke, Mario Raviglione, Sergio Spinaci, Jeroen van Gorkom, Jaap Veen, and Suzanne Verver.

Conflicts of interest: none declared.

Résumé

Interventions destinées à réduire la mortalité par tuberculose et la transmission de l'infection tuberculeuse dans les pays à revenu faible ou moyen

La tuberculose figure parmi les dix causes principales de mortalité à l'échelle mondiale et touche tout particulièrement les pays à faible revenu. Le présent article examine, en passant en revue les publications consacrées à ce sujet, l'impact des mesures de lutte antituberculeuse sur la mortalité par tuberculose et la transmission de l'infection ainsi que les obstacles à la généralisation de ces mesures. Il donne également des estimations de l'efficacité de diverses interventions au moyen d'un modèle proposé par Styblo. Il conclut que le traitement de la tuberculose à frottis positif selon la stratégie OMS de traitement de brève durée sous surveillance directe (DOTS) a de loin le meilleur impact. La vaccination par le BCG, bien que réduisant la mortalité par tuberculose chez l'enfant, n'a probablement qu'une très faible incidence sur la transmission de l'infection. Dans certaines circonstances, on peut attendre un impact supplémentaire sur la mortalité et la transmission par des mesures telles que le traitement des cas à frottis négatif, l'intensification de la recherche des cas de tuberculose à frottis positif et le traitement préventif des patients présentant une co-infection par la tuberculose et le VIH. Parmi ces interventions, le DOTS possède le meilleur rapport coût-efficacité à US $5-40 par année de vie ajustée sur l'incapacité (DALY) gagnée. Le coût de la vaccination par le BCG est probablement inférieur à US $50 par DALY gagnée. Le coût du traitement des patients à frottis négatif par DALY gagnée peut atteindre US $ 100 dans les pays à faible revenu et US $400 dans les pays à revenu moyen. Les autres interventions, par exemple le traitement préventif des patients VIH-positifs, semblent avoir un moins bon rapport coût-efficacité. Le principal obstacle à la généralisation du DOTS est l'absence d'engagement politique, avec pour conséquence une insuffisance des ressources financières et humaines consacrées à la lutte contre la tuberculose. Il semble toutefois, d'après certains signes encourageants, que cette situation s'améliore depuis quelques années. D'autres obstacles sont en rapport avec l'engagement du secteur privé, la réforme du secteur de la santé, la capacité gestionnaire des programmes de lutte antituberculeuse, l'administration du traitement et l'approvisionnement en médicaments. A l'échelle mondiale, la lutte contre la tuberculose pourrait grandement bénéficier des innovations techniques, comme la mise au point d'un vaccin donnant une bonne protection contre la tuberculose pulmonaire à frottis positif chez l'adulte, l'adoption de schémas thérapeutiques plus simples et plus courts pour le traitement de la tuberculose, qu'il s'agisse de l'infection ou de la maladie, et l'amélioration du diagnostic de l'infection et de la maladie.

Resumen

Intervenciones de reducción de la mortalidad por tuberculosis y de la transmisión de esta enfermedad en los países de ingresos bajos y medios

La tuberculosis es una de las 10 causas principales de mortalidad a nivel mundial y afecta en particular a los países de ingresos bajos. En este trabajo se hace una revisión de la literatura para examinar la repercusión de las medidas de lucha contra la tuberculosis en la mortalidad por esta causa y en la transmisión de la enfermedad, así como los obstáculos a la ampliación de dichas medidas. Se ofrecen asimismo estimaciones de la eficacia de diversas intervenciones a partir de un modelo propuesto por Styblo. La conclusión es que el tratamiento de los casos de tuberculosis con frotis positivo mediante la estrategia OMS de tratamiento breve bajo observación directa (DOTS) es de lejos la medida con mayor impacto. La inmunización con BCG reduce la mortalidad infantil por tuberculosis, pero su repercusión en la transmisión de la dolencia es probablemente mínima. En determinadas situaciones, cabe esperar que tengan más impacto en la mortalidad y transmisión el tratamiento de los casos con frotis negativo, la intensificación de la búsqueda de casos de tuberculosis con frotis positivo y el tratamiento preventivo de los individuos con doble infección por tuberculosis y VIH. De estas intervenciones, el tratamiento DOTS es el más eficiente, con un costo de aproximadamente US$ 5-40 por año de vida ajustado en función de la discapacidad (AVAD) ganado. El costo de la inmunización con BCG se sitúa probablemente por debajo de los US$ 50 por AVAD ganado. El tratamiento de los pacientes con frotis negativo tiene un costo por AVAD ganado de hasta US$ 100 en los países de ingresos bajos, y de hasta US$ 400 en los de ingresos medios. Otras intervenciones, como el tratamiento preventivo de los individuos VIH-positivos, son al parecer menos costoeficaces. La principal dificultad con que tropieza la ampliación de la estrategia DOTS es la falta de compromiso político, cuyo resultado es la escasez de fondos y recursos humanos para la lucha contra la tuberculosis. No obstante, en los últimos años hemos podido observar algunos signos alentadores de un mayor compromiso de esa naturaleza. Otras dificultades guardan relación con la participación del sector privado, la reforma del sector de la salud, la capacidad de gestión de los programas contra la tuberculosis, la dispensación de tratamiento y el suministro de medicamentos. La lucha mundial contra la tuberculosis podría beneficiarse sobremanera de diversas innovaciones técnicas, en particular del desarrollo de una vacuna que confiera una buena protección frente a la tuberculosis pulmonar con frotis positivo en los adultos, de regímenes terapéuticos más sencillos y breves para el tratamiento de la enfermedad y de la infección, y de mejores medios diagnósticos para ambas.

References

1. World Health Organization. *The world health report 2000 — Health systems: improving performance.* Geneva: World Health Organization; 2000.
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997;349:1269-76.
3. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *Journal of the American Medical Association* 1999;282:677-86.
4. World Health Organization. *Global tuberculosis control.* Geneva: World Health Organization; 2001. Unpublished document WHO/CDS/TB/2001.287.
5. De Cock KM, Soro B, Coulibaly IM, Lucas SB. Tuberculosis and HIV infection in sub-Saharan Africa. *Journal of the American Medical Association* 1992;268:1581-7.
6. Murray C, Styblo K, Rouillon A. Tuberculosis. In: Jamison JT, Mosley WH, Measham AR, Bobadilla JL, editors. *Disease control priorities in developing countries.* New York: Oxford University Press; 1993. pp. 233-59.
7. Styblo K. *Epidemiology of tuberculosis.* The Hague: Royal Netherlands Tuberculosis Association; 1991.
8. Rieder HL. *Epidemiologic basis for tuberculosis control.* Paris: International Union Against Tuberculosis and Lung Disease; 1999.
9. Grzybowsky S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. *Bulletin of the International Union against Tuberculosis* 1975;50:90-106.
10. Van Geuns HA, Meijer J, Styblo K. Results of contact examination in Rotterdam, 1967-69. *Bulletin of the International Union against Tuberculosis* 1975;50:107-19.
11. Behr MA, Warren SA, Salamon H, Hopewell PC, Ponce de Leon A, Daley CL, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet* 1999;353:444-9.
12. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiology and Infection* 1997;119:183-201.
13. Vynnycky E, Fine PE. Lifetime risks, incubation period, and serial interval of tuberculosis. *American Journal of Epidemiolology* 2000;1(52):247-63.
14. Van Rie A, Warren R, Richardson M, Victor TC, Gee RP, Enarson DA, et al. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. *New England Journal of Medicine* 1999;341:1174-9.
15. Watts J. G8 countries set priorities for infectious diseases but fail to make progress on debt relief. *Bulletin of the World Health Organization* 2000;78:1168.
16. Dye C. Tuberculosis 2000-2010: control, but not elimination. *International Journal of Tuberculosis and Lung Disease* 2000;4(Suppl 2):S146-52.
17. The World Bank. *World development report 1993 —Investing in health.* New York: Oxford University Press; 1993.
18. Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. *Lancet* 1998;352: 1886-91.
19. Dye C, Fengzeng Z, Scheele S, Williams B. Evaluating the impact of tuberculosis control: number of deaths prevented by short-course chemotherapy in China. *International Journal of Epidemiology* 2000; 29:558-64.
20. Suarez PG, Watt CJ, Alarcon E, Portocarrero J, Zavala D, Canales R, et al. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *Journal of Infectious Diseases* 2001;184:473-8.
21. Murray CJL, Salomon JA. Modeling the impact of global tuberculosis control strategies. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95:13881-6.
22. Murray CJL, Salomon JA. Expanding the WHO tuberculosis control strategy: rethinking the role of active case finding. *International Journal of Tuberculosis and Lung Disease* 1998;2(Suppl):S9-15.
23. Raviglione MC, Dye C, Schmidt S, Kochi A, for the WHO Global Surveillance and Monitoring Project. Assessment of worldwide tuberculosis control. *Lancet* 1997;350:624-9.
24. Netto EM, Dye C, Raviglione MC, for the Global Monitoring and Surveillance Project. Progress in global tuberculosis control 1995-1996, with emphasis on 22 high-incidence countries. *International Journal of Tuberculosis and Lung Disease* 1999;3:310-20.
25. Styblo K, Bumgarner JR. Tuberculosis can be controlled with existing technologies: evidence. The Hague: Tuberculosis Surveillance Research Unit; 1991. Progress Report 1991. pp. 60-72.
26. Broekmans J. Control strategies and programme management. In: Porter JDH, McAdam KPWJ, editors. *Tuberculosis — back to the future.* Chichester: John Wiley & Sons; 1994.
27. Harvard Medical School/Open Society Institute. *The global impact of drug-resistant tuberculosis.* Boston (MA): Harvard Medical School; 1999.
28. Jha P, Nagelkerke JD, Ngugi EN, Prasada Rao JV, Willbond B, Moses S, et al. Public health. Reducing HIV transmission in developing countries. *Science.* 2001;292:224-5.
29. Harries AD, Hargreaves NJ, Kemp J, Jindani A, Enarson DA, Maher D, et al. Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1. *Lancet* 2001;357:1519-23.
30. Kochi A. Tuberculosis control — is DOTS the health breakthrough of the 1990s? *World Health Forum* 1997;18:225-32.
31. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. *Lancet* 1998;352:1340-3.
32. Bayer R, Stayton C, Desvarieux M, Healton C, Landesman S, Tsai WY. Directly observed therapy and treatment completion for tuberculosis in the United States: is universal supervised therapy necessary? *American Journal of Public Health* 1998;88:1052-8.
33. Becx-Bleumink M, Djamaluddin S, Loprang F, De Soldenhoff R, Wibowo H, Aryono M. High cure rates in smear-positive tuberculosis patients using ambulatory treatment with once-weekly supervision during the intensive phase in Sulawesi, Republic of Indonesia. *International Journal of Tuberculosis and Lung Disease* 1999;3:1066-72.
34. Volmink J, Matchaba P, Garner P. Directly observed therapy and treatment adherence. *Lancet* 2000;355:1345-50.
35. Walley JD, Khan MA, Newell JN, Khan MH. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomised trial in Pakistan. *Lancet* 2001;357:664-9.
36. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineburg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. *Journal of the American Medical Association* 1994;271:698-702.
37. Fine PE. Bacille Calmette-Guerin vaccines: a rough guide. *Clinical Infectious Diseases* 1995;20:11-4.
38. Behr MA, Wilson MA, Gill WP, Salamon H, Schoolnik GK, Rane S, et al. Comparative genomics of BCG vaccines by whole-genome DNA microarray. *Science* 1999;284:1520-3.
39. Fine PEM. BCG vaccines and vaccination. In: Reichman LB, Hershfield ES, editors. *Tuberculosis — a comprehensive international approach.* New York: Marcel Dekker; 2000. pp. 503-22.
40. Wilson ME, Fineberg HV, Colditz GA. Geographic latitude and the efficacy of bacillus Calmette-Guerin vaccine. *Clinical Infectious Diseases* 1995; 20:982-91.
41. Styblo K, Meijer J. Impact of BCG vaccination programmes in children and young adults on the tuberculosis programme. *Tubercle* 1976;57:17-43.
42. Toman K. *Tuberculosis case-finding and chemotherapy. Questions and answers.* Geneva: World Health Organization; 1979.
43. Lobue PA, Perry S, Catanzaro A. Diagnosis of tuberculosis. In: Reichman LB, Hershfield ES, editors. *Tuberculosis — a comprehensive international approach.* New York: Marcel Dekker; 2000. pp. 341-75.
44. Harries AD, Maher D, Nunn P. An approach to the problems of diagnosing and treating adult smear-negative pulmonary tuberculosis in high-HIV-prevalence settings in sub-Saharan Africa. *Bulletin of the World Health Organization* 1998;76:651-62.
45. World Health Organization. *Treatment of tuberculosis. Guidelines for national programmes.* Geneva: World Health Organization; 1997.
46. Styblo K, Dankova D, Drapela J, Galliova J, Jezek Z, Krivanek J, et al. Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia. *Bulletin of the World Health Organization* 1967;37:819-74.
47. Styblo K, Meijer J. The quantified increase of the tuberculosis infection rate in a low prevalence country to be expected if the existing MMR programme were discontinued. *Bulletin of the International Union of Tuberculosis* 1980;55:3-8.

48. Styblo K, Van Geuns HA, Meijer J. The yield of active case finding in persons with inactive pulmonary tuberculosis of fibrotic lesions. *Tubercle* 1984; 65:237-51.
49. Gothi GD, Narayan R, Nair SS, Chakraborty AK, Srikanataramu N. Estimation of prevalence of bacillary tuberculosis on the basis of chest X-ray and/or symptomatic screening. *Indian Journal of Medical Research* 1976;64:1150-9.
50. Elink Schuurman MW, Srisaenpang S, Pinitsoontorn S, Bijleveld I, Vaeteewoothacharn K, Methapat C. The rapid village survey in tuberculosis control. *Tubercle and Lung Disease* 1996;77:549-54.
51. Aluoch JA, Swai OB, Edwards EA, Stott H, Darbyshire JH, Fox W, et al. Study of case-finding for pulmonary tuberculosis in outpatients complaining of a chronic cough at a district hospital in Kenya. *American Review of Respiratory Disease* 1984;129:915-20.
52. Aluoch JA, Edwards EA, Stott H, Fox W, Sutherland I. A fourth study of case-finding methods for pulmonary tuberculosis in Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1982;76:679-91.
53. Braun MM, Badi N, Ryder RW, Baende E, Mukadi Y, Nsuami M, et al. A retrospective cohort study of tuberculosis among women of childbearing age with HIV infection in Zaire. *American Review of Respiratory Disease* 1991;143:501-4.
54. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *New England Journal of Medicine* 1989;320:545-50.
55. Antonucci G, Girardi E, Raviglione MC, Ippolito G. Risk factors for tuberculosis in HIV-infected persons. A prospective cohort study. The Gruppo Italiano di Studio Tubercolosi e AIDS (GISTA). *Journal of the American Medical Association* 1995;274:143-8.
56. Espinal MA, Perez EN, Baez J, Henriquez L, Fernandez K, Lopez M, et al. Infectiousness of *Mycobacterium tuberculosis* in HIV-1-infected patients with tuberculosis: a prospective study. *Lancet* 2000;355:275-80.
57. Elliott AM, Hayes RJ, Halwiindi B, Luo N, Tembo , Pobee JO, et al. The impact of HIV on infectiousness of pulmonary tuberculosis: a community study in Zambia. *AIDS* 1993;7:981-7.
58. Cauthen GM, Dooley SW, Onorato IM, Ihle WW, Burr JM, Bigler WJ, et al. Transmission of *Mycobacterium tuberculosis* from tuberculosis patients with HIV infection or AIDS. *American Journal of Epidemiology* 1996;44:69-77.
59. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet* 1993;342:268-72.
60. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mgyenyi P, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *New England Journal of Medicine* 1997;337:801-8.
61. Foster S, Godfrey-Faussett P, Porter J. Modelling the economic benefits of tuberculosis preventive therapy for people with HIV: the example of Zambia. *AIDS* 1997;11:919-25.
62. Bell JC, Rose DN, Sacks HS. Tuberculosis preventive therapy for HIV-infected people in sub-Saharan Africa is cost effective. *AIDS* 1999;13:1549-56.
63. Rose DN. Short-course prophylaxis against tuberculosis in HIV-infected persons. A decision and cost-effectiveness analysis. *Annals of Internal Medicine* 1998;129:779-86.
64. Mwinga A, Hosp M, Godfrey-Faussett P, Quigley M, Mwaba P, Mugala BN, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS* 1998;12:2447-57.
65. Fitzgerald DW, Desvarieux M, Severe P, Joseph P, Johnson WD Jr, Pape JW. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. *Lancet* 2000;356:1470-4.
66. Aisu T, Raviglione MC, van Praag E, Eriki P, Narain JP, Barugahare L, et al. Preventive chemotherapy for HIV-associated tuberculosis in Uganda: an operational assessment at a voluntary counselling and testing centre. *AIDS* 1995;9:267-73.
67. Hawken MP, Muhindi DW. Tuberculosis preventive therapy in HIV-infected persons: feasibility issues in developing countries. *International Journal of Tuberculosis and Lung Disease* 1999;3:646-50.
68. Kirk O, Gatell JM, Mocroft A, Pedersen C, Proenca R, Brettle RP, et al. Infections with *Mycobacterium tuberculosis* and *Mycobacterium avium* among HIV-infected patients after the introduction of highly active antiretroviral therapy. EuroSIDA Study Group. *American Journal of Respiratory and Critical Care Medicine* 2000;162:865-72.
69. Girardi E, Antonucci G, Vanacore P, Libanore M, Errante I, Matteeli A, et al. Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. *AIDS* 2000;14:1985-91.
70. Cohn DL, El-Sadr WM. Treatment of latent tuberculosis infection. In: Reichman LB, Hershfield ES, editors. *Tuberculosis – a comprehensive international approach.* New York: Marcel Dekker; 2000. pp. 471-502.
71. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *International Journal of Tuberculosis and Lung Disease* 1999;3:847-50.
72. Berg G. The prognosis of open pulmonary tuberculosis – a clinical-statistical analysis. Lund: Hakan Ohlsson; 1939.
73. Verver S, Bwire R, Borgdorff MW. Screening for pulmonary tuberculosis among immigrants: estimated effect on severity of disease and duration of infectiousness. *International Journal of Tuberculosis and Lung Disease* 2001;5:419-25.
74. Blower SM, Small PM, Hopewell PC. Control strategies for tuberculosis epidemics: new models for old problems. *Science* 1996;273:497-500.
75. Murray CJ, DeJonghe E, Chum HJ, Nyangulu DS, Salomao A, Styblo K. Cost- effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries. *Lancet* 1991;338:1305-8.
76. De Jonghe E, Murray CJL, Chum HJ, Nyangulu DS, Salomao A, Styblo K, et al. Cost-effectiveness of chemotherapy for sputum smear-positive pulmonary tuberculosis in Malawi, Mozambique and Tanzania. *International Journal of Health Planning and Management* 1994;9:151-81.
77. Barnum HN. Cost savings from alternative treatments for tuberculosis. *Social Science and Medicine* 1986;23(9):847-50.
78. Kamolratanakul P, Chunhaswadikul B, Jittinandana A, Tangcharoensathien V, Udomrati N, Akksilp S. Cost-effectiveness analysis of three short-course anti-tuberculosis programmes compared with a standard regimen in Thailand. *Journal of Clinicial Epidemiology* 1993;46(7):631-6.
79. Joesef MR, Remington PL, Tjiproherijanto P. Epidemiological model and cost-effectiveness analysis of tuberculosis treatment programmes in Indonesia. *International Journal of Epidemiology* 1989;18(1):174-9.
80. Saunderson P. An economic evaluation of alternative programme designs for tuberculosis control in rural Uganda. *Social Science and Medicine* 1995;40(9):1203-12.
81. Floyd K, Wilkinson D, Gilks CF. Costs and cost-effectiveness of community-based DOTS vs conventional treatment in Africa. *British Medical Journal* 1997;315:1407-11.
82. Wilkinson D, Floyd K, Gilks CF. Costs and cost-effectiveness of alternative tuberculosis management strategies in South Africa – implications for policy. *South African Medical Journal* 1997;87:451-5.
83. Floyd K, Sinanovic E, Nganda B, Okello D, Skeva J, Maher D, et al. Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in sub-Saharan Africa: evidence from 5 pilot projects (unpublished data).
84. Murray CJL, Styblo K, Rouillon A. Tuberculosis in developing countries: burden, intervention and cost. *Bulletin of the International Union of Tuberculosis and Lung Disease* 1990;65:2-20.
85. Shepard DS, Agness-Soumahoro, Bail RN, Campino AC, Iunes RF, Izazola JA, et al. Expenditures on HIV/ AIDS: levels and determinants lessons from five countries. Proceedings of World Bank/European Union/UNAIDS Conference on AIDS and Development: the Role of Government, Limelette, Belgium, 17–19 June 1996.
86. World Health Organization. *Report of the ad hoc committee on the tuberculosis epidemic. London, 17–19 March 1998.* Geneva: World Health Organization; 1998.
87. Report on the Ministerial Conference on Tuberculosis and Sustainable Development, Amsterdam, Netherlands, 22–24 March 2000. Available at: URL: http://www.stoptb.org/conference/default.asp
88. World Health Organization. *Status of tuberculosis in the 22 high-burden countries.* Geneva: World Health Organization; 1999. Unpublished document WHO/CDS/TB/99.271.
89. World Health Organization. *Involving private practitioners in tuberculosis control: issues, interventions, and emerging policy framework.* Geneva: World Health Organization; 2001. Unpublished document WHO/CDS/TB/ 2001.285.
90. Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. *Lancet* 2001;358:912-6.

91. Lonnroth K. Public health in private hands. Studies on private and public tuberculosis care in Ho Chi Minh City, Vietnam. Gothenburg: Gothenburg University and Nordic School of Public Health; 2000.
92. Miller B. Health sector reform: scourge or salvation for TB control in developing countries? *International Journal of Tuberculosis and Lung Disease* 2000; 4:593-4.
93. Baris E. Tuberculosis in times of health reform. *International Journal of Tuberculosis and Lung Disease* 2000;4:595-6.
94. Weil DEC. Advancing tuberculosis control within reforming health systems. *International Journal of Tuberculosis and Lung Disease* 2000;4:597-605.
95. Kumaresan JA, de Colombani P, Karim E. Tuberculosis and health sector reform in Bangladesh. *International Journal of Tuberculosis and Lung Disease* 2000;4:615-21.
96. Hanson C, Kibuga D. Effective tuberculosis control and health sector reforms in Kenya: challenges of increasing tuberculosis burden and opportunities through reform. *International Journal of Tuberculosis and Lung Disease* 2000;4:627-32.
97. Bosman MJC. Health sector reform and tuberculosis control: the case of Zambia. *International Journal of Tuberculosis and Lung Disease* 2000; 4:606-14.
98. Kritski AL, Ruffino-Netto A. Health sector reform in Brazil: impact on tuberculosis control. *International Journal of Tuberculosis and Lung Disease* 2000;4:622-6.
99. Khatri GR, Frieden TR. The status and prospects of tuberculosis control in India. *International Journal of Tuberculosis and Lung Disease* 2000;4: 193-200.
100. Girardi E, Raviglione MC, Antonucci G, Godfrey-Faussett P, Ippolito G. Impact of the HIV epidemic on the spread of other diseases: the case of tuberculosis. *AIDS* 2000;14(Suppl 3):S47-56.
101. Cole ST, Brosch R, Parkhill J, Garnier T, Churcher C, Harries D, et al. Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature* 1998;393:537-44.
102. Pym AS, Cole ST. Post DOTS, post genomics: the next century of tuberculosis control. *Lancet* 1999;353:1004-5.