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Contents

SUMMARY

Tuberculosis is among the top ten causes of global morbidity and mortality. It affects in particular low-income countries, with the highest case rates in Africa and the highest case numbers in Asia. *Mycobacterium tuberculosis* has man as its principal reservoir, and is mainly transmitted by patients with smear-positive pulmonary tuberculosis. The main tuberculosis control strategy (the WHO DOTS strategy) aims at diagnosis and treatment of smear-positive tuberculosis patients self-reporting to the health services. In addition, BCG vaccination is applied widely.

Additional strategies which may be considered are diagnosis and treatment of self-reporting patients with smear-negative tuberculosis; active case-finding and treatment of smear-positive tuberculosis; and preventive therapy of tuberculosis infection in the following target groups: HIV-infected individuals, contacts of tuberculosis cases, and adults with latent infection in the general population. Multi-drug-resistant tuberculosis may require a special response in countries where it occurs frequently.

This paper estimates the impact on mortality and transmission of these control measures and confirms that with currently available tools the WHO DOTS strategy has by far the highest impact. Though BCG reduces childhood tuberculosis mortality, its impact on tuberculosis transmission is probably minimal.

Additional impact on mortality and transmission may be expected from treatment of smear-negative tuberculosis and from intensifying case finding of smear-positive tuberculosis in settings where cure rates are high and case detection rates low. In countries with a high prevalence of HIV infection, some additional impact may be expected from preventive therapy among individuals with dual TB-HIV infection. Contact tracing followed by preventive therapy among infected contacts, though beneficial to the individuals concerned, is expected to have little impact at the population level. Treatment of latent infection among

adults in the general population would theoretically avert a large number of cases over the next decades, but may not be feasible with available technology.

Existing evidence indicates that the most cost-effective intervention is DOTS for new smear-positive patients, which is likely to be under US$40 per DALY and, in some cases, under US$10. BCG is likely to be less than US$50 per DALY. DOTS for smear-negative patients is probably in the region of US$10-20 per DALY in low income settings, and around US$100 in middle-income countries. Other interventions, such as those for MDR-TB and preventive therapy for HIV+ individuals, appear less cost-effective.

The major constraint to scaling up the available tuberculosis control interventions is lack of political commitment, resulting in shortages of funding and human resources for tuberculosis control. However, in recent years there are 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 (1) a vaccine giving good protection against smear-positive pulmonary tuberculosis in adults; (2) drug regimens for treatment of tuberculosis disease and latent infection requiring fewer contacts between patient and the health service and/or a shorter duration of treatment; and (3) tools allowing better and easier diagnosis of tuberculosis infection and disease.

Introduction

The WHO DOTS strategy is widely accepted as a very cost-effective health intervention (1). If applied widely, it may have a large impact on the global tuberculosis situation (2). However, it is recognised that this impact will take decades to achieve (2,3,4). Reasons for this slow progress include the slow epidemiology of tuberculosis itself, and the slow speed at which the DOTS strategy is spreading in the world (5,6).

Recently, the G8 has called for scaling up interventions against HIV, tuberculosis and malaria aiming at a reduction of tuberculosis mortality by 50% by 2010. With the DOTS strategy alone, this target may be difficult to achieve (7). Therefore, it may be worth exploring to what extent additional impact can be expected from additional tuberculosis control measures.

The present paper aims at exploring the effectiveness and cost-effectiveness of various tuberculosis control measures as well as constraints to scaling up these interventions. The paper is structured in five main parts. First we summarise the natural history and epidemiology of tuberculosis, followed by a description of the main intervention options available. The third part assesses what impact each intervention has on tuberculosis mortality and transmission at the level of the individual patient, as well as at the population level in the short term, using a simple model approach. Part three also summarises evidence on the cost-effectiveness of these interventions. Part four discusses constraints to scaling up the diagnosis and treatment of symptomatic patients reporting to the health serves and part five constraints to scaling up the other interventions.

1. Tuberculosis disease burden, natural history, and trend in human populations

Tuberculosis disease burden

Tuberculosis is among the top ten causes of global mortality and morbidity (8,9). Recently published estimates suggest that 32% of the world's population is infected with the tubercle bacillus, that tuberculosis disease incidence is in the order of 8 million new cases per year, and that 1.8 million people die of tuberculosis each year (10,11).

Tuberculosis is distributed very unevenly over the world: the highest incidence rates are found in the WHO Regions Africa (259/100,000) and Southeast Asia (202/100,00), with intermediate rates in the Eastern Mediterranean (129/100,000) and Western Pacific Regions (120/100,000) and the lowest rates in Europe (51/100,000) and the Americas (52/100,000) (10) (Figure 1). The largest *numbers* of tuberculosis cases are found in the WHO Regions Southeast Asia (2,948,000), Western Pacific (1,982,000), and Africa (1,586,000) (10). Of the approximately 8 million new tuberculosis cases occurring each year, around 80% are found in only 22 countries (10,11)[1]. (Figure 2). The tuberculosis situation has very much worsened over the past two decades in Africa, due to the HIV epidemic and in Eastern Europe in association with multi-drug resistance (11,12).

Natural history

Tuberculosis is caused by *Mycobacterium tuberculosis*, a microorganism whose principal reservoir is man. *M. tuberculosis* is spread mainly by patients with infectious, pulmonary tuberculosis when they cough or sneeze (13-15). When these bacilli are inhaled, they may lead to infection. After infection, most people do not develop tuberculosis disease. The exact proportion developing disease (in the absence of preventive therapy) depends amongst others on the age at infection, but is often estimated at approximately 10%-12% (15-17). The

[1] In the latest WHO report, the list of high burden countries comprises 23 countries (11).

incubation period of tuberculosis (the period between infection and onset of disease) is highly variable and ranges from a few weeks to many decades. The risk of developing disease declines steeply with time after infection. Conventionally, disease within five years after infection (i.e. when disease risk is highest) is called primary tuberculosis (14,16). Disease occurring after more than five years since first infection may be due to reactivation or to reinfection (14-18). Latent infection confers partial immunity, resulting in a lower risk of disease after re-infection than after primary infection (14,15).

Tuberculosis disease may affect the lungs (pulmonary tuberculosis), other organs (extrapulmonary tuberculosis) or both. The number of bacilli that patients cough up in their sputum varies among patients. If there are more than 5,000-10,000 bacilli per millilitre of sputum they can be detected by examination of a sputum smear under the microscope (19). These smear-positive patients are responsible for most tuberculosis transmission although some transmission is attributable to smear-negative patients (20-22). In addition, although the majority of patients developing smear-positive tuberculosis do so within six months after the onset of illness, others may take longer (23). Thus some patients with smear-negative tuberculosis may progress to smear-positive tuberculosis in the absence of treatment (23). Of all tuberculosis patients, approximately 80% have pulmonary tuberculosis and of the patients with pulmonary tuberculosis, approximately 50% are smear-positive (24).

In the absence of treatment, tuberculosis has a high case fatality rate. In earlier reviews the case fatality rate was estimated at 60 to 70 percent for smear-positive pulmonary tuberculosis, and 40 to 50 percent for other forms of tuberculosis (13,15). The latter percentage depends strongly on the site. For instance, tuberculosis lymphadenitis is relatively benign, while tuberculosis meningitis has a case fatality rate of close to 100% (13,15).

Risk factors for tuberculosis

Risk factors for tuberculosis can be separated into risk factors for exposure, risk factors for infection given exposure, risk factors for progression from tuberculosis infection to disease, and risk factors for tuberculosis mortality given disease (15). For an extensive discussion we refer to relevant monographs (14,15). Here, we will limit the discussion of risk factors to a few very important ones.

Age is a very important risk factor for tuberculosis, as it plays a role in all stages from exposure to mortality. Exposure to tuberculosis source cases depends on social mixing patterns, and thus on the ages of the source cases and their contacts (25,26). Tuberculosis infection prevalence, i.e. the probability of being infected at some time during one's life, increases with age (14). As a result, the risk of reactivation disease increases with age, and (other things being equal) the risk of primary tuberculosis declines (14). Progression from tuberculosis infection to pulmonary tuberculosis disease is also strongly age dependent, as is the proportion of pulmonary tuberculosis patients with smear-positive disease (16,17). Smear-positive pulmonary tuberculosis usually occurs among patients aged 15 years and over. Before the chemotherapy era, tuberculosis mortality rates were highest in young adults (27). However, this represents the overall, combined effect of all steps from exposure to death.

Tuberculosis is diagnosed more often in men than in women in most countries of the world (28-30). The main explanation appears to be that tuberculosis occurs more often in men than in women, since the sex ratio in notified cases is generally similar to the sex ratio in prevalent cases (31). This epidemiological sex difference may result from differences in exposure, risk of infection, and/or rates of progression from infection to disease (28-30).

As is clear from the overview presented above, tuberculosis incidence rates vary strongly between countries, making country of residence a very important risk factor. This has

implications both for global health policy (where particular efforts are directed towards the 22 high-burden countries) and for understanding the impact of migration. In low prevalence countries an increasing proportion of tuberculosis cases is found among the foreign born (32-34). As a result, elimination of tuberculosis in low prevalence countries depends in part on the progress made in the control of tuberculosis in high prevalence countries (34-36).

Poverty is associated with tuberculosis not only when comparing countries, but also within countries (15,37). The association between socioeconomic status and tuberculosis arises in a variety of ways. Exposure is associated with crowding (amongst others depending on household size) and quality of housing (light, ventilation), both of which may be associated with socioeconomic status. Moreover, social mixing is associated with socioeconomic status, perpetuating unequal disease distributions. Progression from infection to disease may depend on nutritional status and thus on poverty. The duration of infectiousness of source cases depends on access to adequate health care, which in many countries depends in part on socioeconomic status. And finally, it is costly to have tuberculosis both at the individual and household level, and at aggregate level (e.g. country). Direct medical costs and indirect costs due to loss of income are high because the disease is serious, requires a relatively long treatment, and strongly increases the risk of death, often in the age group 15-44 years. Thus, not only are the poor more likely to get tuberculosis, tuberculosis itself contributes to poverty (38-43)

HIV infection is the strongest known risk factor for progression from tuberculosis infection to disease (12,14,15,44). HIV infected persons developing tuberculosis have a higher probability of developing extrapulmonary disease or smear-negative pulmonary tuberculosis, but their incidence rate of smear-positive tuberculosis is strongly increased as well (12). The consequences of the HIV epidemic are very clearly seen in Africa where dual infection with *M. tuberculosis* and HIV is common (12,44). Incidence rates of smear-positive tuberculosis

have risen dramatically in countries with a high prevalence of HIV infection (44,45). As the infectiousness of HIV-infected tuberculosis cases is only slightly less than that of non-HIV-infected tuberculosis patients (46-48), the risk of tuberculosis infection may increase as well in these countries, leading to a deterioration of the tuberculosis situation among those without HIV infection as well (49). The impact of the HIV epidemic may be particularly serious if there is no good tuberculosis control programme in place (50,51).

Relatively little is known about genetic risk factors for susceptibility to tuberculosis infection or disease in man. In West Africa, certain variations in the *NRAMP1* gene were shown to be associated with tuberculosis (52). With the rapid progress being made in knowledge of the human genome, more genetic risk factors are likely to become known and these may help to explain differences in tuberculosis epidemiology among populations.

Trend of tuberculosis in human populations

At present the tuberculosis burden mainly affects low-income countries. However, this has not always been so. In the beginning of the 20th century, tuberculosis incidence and mortality rates were higher in Western Europe than they are now in most developing countries (13,14). In Europe and the United States the tuberculosis problem declined moderately between 1900 and 1950, and more steeply thereafter (14,53,54). The steep decline since 1950 is generally attributed to the introduction of anti-tuberculosis chemotherapy. For the moderate decline between 1900 and 1950 various explanations have been proposed including general socioeconomic development (associated with reduced crowding, better housing, smaller household size, and improved nutrition), isolation of infectious patients in sanatoria, and reduced susceptibility of the population due to natural selection (14,15). In many developing countries no evidence is found of a ‘natural’ decline of the tuberculosis problem in the absence of effective interventions (13,14).

The trend of tuberculosis in a human population is determined by the basic and effective reproduction number (or reproductive rate) (55-57). The basic reproduction number is the average number of infectious cases generated if a single infectious case were introduced in a totally susceptible population, while the effective or net reproduction number is the average number of infectious cases generated by a single infectious case in a given population (57). In a stable endemic situation, the average infectious case generates one new infectious case, and thus the effective reproduction number equals 1 (55). Frost was one of the first to recognise that the aim of tuberculosis control is to ensure that the average infectious case generates less than one new infectious case: if that situation can be maintained for long enough, tuberculosis will be eliminated (58).

Although the concept of the basic reproduction number is extremely useful for making projections of the impact of control measures, for tuberculosis its estimation is complicated and its interpretation is not straightforward (57). Recently, reproduction numbers of tuberculosis have been estimated from notification data in the UK (57) and using data from DNA fingerprinting in The Netherlands (35). In the UK, the basic reproduction number has declined from approximately 3 in the year 1900 to below 1 after 1960; the effective reproduction number was 1 in the period 1900-1950 and declined rapidly thereafter (57). In the Netherlands, the effective reproduction number associated with rapid progression was estimated at approximately 0.3 in recent years based on results of DNA-fingerprinting (35).

While the tuberculosis trend in Europe and the United States could be measured by the trend in disease-specific mortality rates and/or tuberculosis notification rates, this may not be possible in many countries with less reliable registration systems. Instead, it may be necessary to use other indicators such as: the trend in the risk of tuberculosis infection (59-61), or the trend in tuberculosis prevalence rates (62,63). Related indicators of the trend of the tuberculosis problem which have been used much less widely include the number of

infections per prevalent case (this is the effective contact rate) (64), the number of infections per notified case (51), shifts in the age distribution of notified tuberculosis cases over time (as a declining trend is associated with an increasing average age of tuberculosis cases (15,55)), and the proportion of cases being clustered according to RFLP-typing using IS*6110* as a probe (65-67).

2. Tuberculosis intervention options

Once we understand the natural history of tuberculosis, it is clear that various interventions may reduce the risk of tuberculosis infection, disease and/or death. For instance, treatment of infectious tuberculosis patients not only reduces their mortality, but also reduces the risk of infection (and thus future cases among other people) by shortening their infectious period. Other interventions, such as preventive therapy and BCG vaccination, reduce the risk of progression from infection to disease, and thus prevent future cases directly in the persons being treated or vaccinated. First, we will present the intervention options currently accepted as global policy (diagnosis and treatment of smear-positive tuberculosis and BCG vaccination), followed by a discussion of possible additional interventions (diagnosis and treatment of smear-negative tuberculosis; preventive therapy of persons with HIV infection, infected contacts of tuberculosis patients, and infected adults in the general population; and interventions to deal with multi-drug resistant tuberculosis).

Diagnosis and treatment of smear-positive tuberculosis

The current global strategy for control of tuberculosis is the DOTS strategy promoted by WHO. The DOTS strategy is based on the insights that treatment of smear-positive cases is vital for breaking the chain of transmission (68), that the major determinant of treatment outcome is that patients take their anti-tuberculosis drugs as prescribed (69), that the best treatment results are obtained using regimens with multiple drugs, including isoniazid and rifampicin (70), and that tuberculosis control through diagnosis of self-reporting symptomatic patients and their treatment is feasible and cost-effective on a national scale in low income countries if accompanied by a strong surveillance and monitoring system (71-73). In 1993,

short course chemotherapy of tuberculosis was listed among the most cost-effective health interventions by the World Bank (1).

The main components of the DOTS strategy are: political commitment, case detection among self-reporting patients with complaints through the use of sputum smear microscopy, short course chemotherapy under proper management conditions, including directly observed therapy, assurance of a regular drug supply, and a strong surveillance and monitoring system, including monitoring of treatment outcomes (74,75). Reliance on smear microscopy ensures that efforts are directly towards the most infectious patients with bacteriologically confirmed tuberculosis. Short course chemotherapy uses a combination of anti-tuberculosis drugs, including rifampicin and isoniazid (the two strongest drugs currently available), and requires 6-8 months to complete treatment. Short-course chemotherapy has consistently been found to be more cost-effective than the longer regimens without rifampicin (76).

The need for directly observed treatment (DOT) as an essential element of the DOTS strategy is controversial. DOT was found to be more cost-effective than self-administered treatment in a range of studies (77-81). However, if adequate treatment outcomes can be achieved without DOT, DOT may be less cost-effective than this alternative (82). A major point of debate is the extent to which the success of tuberculosis control programmes should be attributed to DOT as opposed to other programme elements to promote treatment completion (83-92). For instance, a recent review suggests that the success of DOTS may depend more on other components of this strategy than on DOT (90).

A vital and non-controversial element of the DOTS strategy is the importance given to monitoring treatment outcomes. As treatment duration is long and patients generally improve rapidly early on, special efforts are required to ensure treatment completion. Thus, good treatment outcomes can not be assumed but need to be ascertained. The DOTS strategy aims

at detecting at least 70% of new smear-positive tuberculosis cases and at a treatment success of 85% among these patients (11).

BCG vaccination

Although BCG is the most widely used vaccine, its effectiveness has been controversial for many years (93-107). It is now generally agreed that the protective efficacy of BCG varies between studies with good protection in the order of 80% found in some, and no protection found in others. Various explanations for this have been proposed, including differences in the prevalence of infection with environmental mycobacteria (98,104,105) and differences between BCG strains (101,103).

BCG probably gives good protection (in the order of 75-80%) against disseminated tuberculosis in childhood, including tuberculosis meningitis (98). The number of deaths prevented per child vaccinated depends on the risk of tuberculosis infection. Protection against pulmonary tuberculosis varies, but has been shown to be negligible in India and Malawi (99,106). Unfortunately, these two countries may be more representative of countries with a high incidence of tuberculosis than others where BCG was shown to be more effective. The impact of BCG on tuberculosis transmission is probably very limited. BCG is given at birth, 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 (98,107).

BCG is not included below in the comparison of effectiveness and listing of constraints. The purpose of those sections is to provide an overview of what can be done to scale up tuberculosis control. BCG has already been scaled up. However, its major limitation is its generally low effectiveness as a tuberculosis control measure.

Diagnosis and treatment of smear-negative tuberculosis

Most tuberculosis control programmes provide treatment to smear-negative patients as well as to smear-positive patients. In countries with a high prevalence of HIV infection, the need to deal with smear-negative tuberculosis patients is felt more urgently, as pulmonary tuberculosis patients with HIV infection have a higher probability of being smear-negative (108). Unfortunately, the diagnosis of smear-negative tuberculosis is difficult to make. Patients with pulmonary tuberculosis and without immunodeficiency generally have abnormal chest X-rays (24). However, important limitations of chest X-rays for diagnosing tuberculosis are their lack of specificity and limited inter-reader repeatability (109). Moreover, in patients with HIV infection, the chest X-ray may be normal despite active tuberculosis (24,108). Thus, programmes often employ diagnostic algorithms, which require that tuberculosis suspects with a negative smear are first treated with antibiotics ineffective against tuberculosis. Only after this treatment has failed, (or in critically ill patients) is tuberculosis treatment started (110).

Active case finding and treatment of smear-positive tuberculosis

As the case detection rate is an important determinant of the success of a DOTS programme, using additional methods to improve case detection would seem an obvious extension of this strategy. The DOTS strategy focuses on patients presenting themselves at the health services with complaints, while active case finding involves a special effort by the health service to detect cases, e.g. among contacts of patients, among certain risk groups such as prisoners or the homeless, or in the general population. Although this distinction seems clear, in practice there is a spectrum of case finding methods, along which there is no clear cut-off point between “active” and “passive” case finding. For instance the use of information campaigns

in the general population to encourage symptomatic patients to report to the health service or the use of tuberculosis scouts at outpatient clinics is a mixture of “active” and ”passive” case finding strategies.

Previous experience of active case finding suggests various limitations. In countries with high case detection rates, the contribution of active case finding to reducing transmission was limited (111-113). In programmes with low cure rates, improving the cure rate of cases detected is clearly the top priority. In countries with low case detection rates, perhaps due to limited resources for the public health services, resources for active case finding may be difficult to obtain as well. However, if cure rates are high and case detection rates appear to be low, active case finding may be worth exploring, as mathematical models suggest large potential benefits (3,4).

General population surveys using mass miniature radiography (MMR) have been used as a control method in industrialised countries, and may be expected to detect more than 90% of prevalent cases participating in the survey. However, their cost is high. Population surveys using TB symptoms to screen patients would be much easier and less costly to implement. A drawback is that they may detect only 70% of prevalent tuberculosis cases (114). This proportion is likely to vary according to target group and their perception of cough, as well as on methods used for eliciting symptoms (115). Patients that are detected using this method may have somewhat more advanced disease than those detected through X-ray, as in the former group a-symptomatic patients are detected as well (116,117). Identification of TB suspects in rural areas through village leaders, though much less costly to implement, may yield relatively many TB patients already known by the health services, and far less than 50% of all prevalent cases (118-121).

Mass campaigns (e.g. on an annual basis) to encourage all people with a chronic cough to report for examination to the health service, might be another option but as yet does not

appear to have been evaluated. Although in Kenya the yield of re-examination of previously treated tuberculosis patients was high (121), this may no longer hold since short course chemotherapy is likely to have lower relapse rates. Since 80-90% of prevalent tuberculosis patients found in surveys in Kenya had reported to the health service without being diagnosed, intensifying case finding at outpatients departments would appear a logical other option (121). Indeed, the yield of intensified case finding among patients with respiratory symptoms at an outpatient department was high during a study (122), but routine application of a chronic cough register had disappointing results (121). Further work to evaluate this option is needed.

Preventive therapy in persons with HIV infection

HIV infected people who are also infected by *M. tuberculosis* are at a very strongly increased risk of developing active tuberculosis (123). Whereas the *lifetime* risk of developing tuberculosis after infection in those without HIV infection is in the order of 12% (17), the *annual* risk in those with HIV infection is in the order of 8% (12,124). This risk increases with advancing immunodeficiency (125). As a result, a large proportion of tuberculosis patients in countries affected by the HIV epidemic have HIV co-infection (45). It is clear, therefore, that in countries with a high or rising prevalence of HIV infection, primary prevention of HIV infection is of major importance for tuberculosis control.

In addition. there is now fairly extensive evidence on the efficacy of preventive therapy in those found to have dual TB-HIV infection (126-129). Six months of isoniazid is expected to reduce tuberculosis incidence in those with dual infection by approximately 60%, and 12 months may reduce it by approximately 80% (127-129). These protective efficacies are in the same range as those observed in immunocompetent individuals (130,131). A similar

protective efficacy of 80% was observed in HIV infected patients who had completed their tuberculosis treatment and then received post-treatment isoniazid prophylaxis (132). However, the duration of protection may be shorter in HIV infected individuals, depending on whether elimination of infection can be achieved and on the risk of reinfection. If protection declines after three years and reaches nil by five years, approximately 25% of expected tuberculosis cases would be prevented after a single course of treatment (129). Alternative short-course regimens may be considered as well, such as two months of rifampicin and pyrazinamide (129,133).

Another intervention might be the application of highly active, anti-retroviral therapy (HAART). Since this therapy slows down disease progression and the development of immunodeficiency in HIV infected persons, it may also delay the onset of tuberculosis. Indeed, in recent trials, HAART therapy has been shown to reduce the incidence of tuberculosis (134,135). However, this effect may be temporary only. Reducing the lifetime risk of tuberculosis in HIV infected persons may require specific anti-tuberculosis preventive therapy.

Preventive therapy in contacts of tuberculosis patients

As the risk of developing tuberculosis declines steeply with time since infection, those recently infected might be a target group in which preventive therapy is particularly rewarding. However, there may be major problems in identifying a substantial number of contacts. In contact investigations in high prevalence countries, the probability that tuberculosis infection in a contact is attributable to the index case is much higher in children than in adults, as the prevalence of infection in all adults tends to be high. Thus, contact investigations are often limited to children. Preventive therapy with isoniazid is an effective

method to reduce the risk of disease among these recently infected children by 60%-80% (131). Side effects of preventive therapy in children are rare (131).

Preventive therapy in adults with latent infection

Preventive treatment in adults with latent tuberculosis infection has a protective efficacy in the range of 60-80%, depending on the duration of therapy (130,131). Effectiveness in routine practice may be limited by partial uptake and compliance. Partial uptake and compliance is perhaps understandable, as the lifetime risk for developing tuberculosis due to reactivation in an adult with latent tuberculosis infection is generally less than 5%.

Interventions to deal with multi-drug resistant tuberculosis

An important complication of tuberculosis control is the development of drug resistance when inappropriate treatment is given (136). Drug resistant strains arise through spontaneous mutations. Poor treatment may eliminate drug susceptible strains and select the drug-resistant ones, thus causing acquired drug resistance (137). If patients develop tuberculosis after having been infected with a drug-resistant strain, this is called primary drug resistance. Drug resistance in patients reporting no previous treatment is likely to be primary resistance, and drug resistance in patients having been treated previously is more likely to be acquired. However, the latter group may have had primary resistance during their first episode. Moreover, the previous episode may have been due to a different strain, in particular in areas where reinfection is common (138).

Resistance against isoniazid and rifampicin (i.e. the two most powerful antituberculosis drug currently available) is called multi-drug resistance. Global drug resistance surveillance has identified some countries in which primary multi-drug resistance is common (136,137,139). Treatment outcomes of multi-drug resistant tuberculosis under short course chemotherapy are

generally much worse than those of drug susceptible tuberculosis (140), while second-line drug regimens are complex, very costly, and sometimes toxic (141).

In recent years, there has been extensive debate on the measures needed to deal with the problem of multi-drug resistance (141-143). There is consensus that in countries with low levels of multi-drug resistance its emergence can and should be prevented through effective tuberculosis control programmes (141,143,144). Restricting the use of rifampicin to these programmes would be an important supporting measure. However, if high levels of multi-drug resistance are present, additional measures are required, such as the DOTS-plus strategy (141). There is limited evidence that drug-resistant tuberculosis strains are transmitted somewhat less than drug sensitive strains (66,145,146). However, in order to reduce the size of the problem of multi-drug resistance, this is unlikely to be sufficient and high cure rates are needed (143). Unfortunately, in situations where drug resistance is common, cure rates have been low, as those low cure rates generated the resistance problem in the first place. Adding more drugs in such situations is likely to generate further drug resistance. Thus, it has been proposed to consider 'hot spots' of multi-drug resistance as international public health emergencies requiring huge financial and human resources (141).

The remainder of this paper focuses on how to deal with drug-susceptible tuberculosis. In countries with low levels of multi-drug resistance this will largely suffice for decision making. However, if drug resistance increases, both the effectiveness of case finding and treatment, and the effectiveness of preventive therapy will decrease. For the special measures to be considered in those circumstances, we refer to other reviews (141).

3. Effectiveness and cost-effectiveness of interventions aiming at reducing tuberculosis mortality and transmission

Mortality reduction in persons being treated

The impact of treatment of smear-positive tuberculosis cases on mortality is impressive. Without treatment, 60-70% of smear-positive tuberculosis patients would die within a few years. With short course chemotherapy, applied under programme conditions in developing countries, the case fatality ratio can be reduced to approximately 5% (147). Although in various African countries the case fatality ratio is now much increased, these additional deaths are attributable to HIV rather than tuberculosis (148).

The direct health impact of treating smear-negative tuberculosis patients is also considerable. Without treatment, the case fatality ratio would be in the order of 20% in those without immunodeficiency (15). With treatment, the case fatality ratio was well below 5% in trials using a 12 month regimen without rifampicin (149). Results with rifampicin containing regimens should be even better. Under programme conditions, mortality is likely to be somewhat higher than in a clinical trial, but gains would still be considerable. As advancing immunodeficiency associated with HIV infection strongly increases case fatality both in those treated and those not treated (150), the impact on life-years gained is likely to be much smaller in this group (151).

The direct health impact of active case finding may be substantial for patients who would otherwise not have been detected. However, precise estimates do not appear to be available. In patients who would otherwise have been detected through self-reporting, the health impact of active case finding may be measured by prevention of severe disease and improved treatment outcome, as patients detected earlier are likely to have less serious disease (117). However, since treatment outcome is generally favourable in self-reporting patients, the additional direct health impact of active case finding is likely to be limited.

The impact of preventive therapy on mortality can only be estimated very crudely. The number of tuberculosis cases prevented can be estimated, although estimates depend partly on the importance of reinfection, which in turn depends on the risk of infection. More

importantly, the average risk of death of tuberculosis cases would depend on their age at onset of disease, the proportion of cases being detected and the cure rate of the programme at that time. Clearly, the poorer the programme is in detecting and curing patients, the higher the impact of preventive therapy on mortality for each case prevented. However, poor programmes are unlikely to effectively deliver preventive therapy. Therefore, we assume that preventive therapy will only be considered by programmes with high case detection and cure rates of smear-positive tuberculosis. For convenience, but admittedly extremely crudely, below we assume that for each tuberculosis case prevented, 0.1 death is prevented.

Preventive therapy in HIV-infected persons would prevent an estimated 25% of expected tuberculosis cases in this group. Its impact on mortality is assessed in a separate paper on interventions to reduce HIV-asociated mortality, since these deaths are not counted as tuberculosis mortality.

The impact on mortality of preventive therapy among children who are contacts of tuberculosis patients is estimated as follows. If the life-time risk of developing tuberculosis were 12%, then a six-months course of isoniazid with a protective efficacy of 60% would on average prevent 0.07 tuberculosis cases and 0.007 tuberculosis deaths. Among adults with latent infection, the lifetime risk of developing tuberculosis may be 3%, and preventive therapy would thus prevent at most 0.018 tuberculosis cases and 0.0018 tuberculosis deaths. However, the side effects asociated with preventive therapy need to be taken into account as well. In particular, hepatitis is a feared complication which occurs in 0.1-1% of those taking isoniazid and may lead to death (130,131). An overview of the estimated impact of tuberculosis control measures on mortality is shown in Figure 3.

Avoiding first generation infectious cases

Each infectious tuberculosis case prevented by a certain tuberculosis control method also prevents the infectious cases which would have been generated by that case and the cases generated by those secondary cases, etc. As this further effect applies approximately equally to all cases prevented around the same time period in the same country, this paper compares the impact of interventions on transmission by comparing the number of infectious cases they prevent directly, i.e. first generation cases only.

The impact of DOTS on transmission may be estimated following the reasoning of Styblo (147,152). In other words, it can be assumed that in the absence of treatment the duration of the infectious period is two years and that each tuberculosis case would generate 2 ß infections (where ß is the effective contact rate), one of which - in an endemic situation - would progress to infectious tuberculosis. Each new self-reporting case detected after on average 4 months would have infected 0.33 ß contacts. In addition, assuming a relapse rate of 15% and again 4 months delay before the relapsed case is put on treatment, another 0.05 ß infection is generated. Finally, if each failure case remains infectious for 3 years, s/he would infect a further 3 ß contacts. With a failure rate of 5%, this would add on average another 0.15 ß infections per new case. Thus, according to these assumptions, a good DOTS programme could reduce the number of infections per case from 2 ß to 0.53 ß, 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 this DOTS programme would prevent 0.73 new infectious cases.

Treatment of smear-negative tuberculosis patients has much less impact on transmission than treatment of smear-positive patients. The number of infections and secondary cases generated by a case with smear-negative pulmonary tuberculosis is approximately 10-20% of the numbers generated by a case with smear-positive tuberculosis (20-22). Thus, if each smear-

positive case treated under DOTS would prevent 0.7 future case, each smear-negative case treated under the same conditions might prevent 0.1 future cases.

For active case finding, if the screening interval were longer than the average duration of infectiousness, patients would be detected at a random point in time, and their duration of infectiousness would on average be reduced by 50%. For patients who would otherwise have been detected through self-reporting, this implies that instead of the 0.53 ß infections they would have generated, those detected actively would generate 0.37 ß infections, as the initial 0.33 ß infections are cut by 50%. Therefore, the additional benefit to detection through self-reporting is 0.16 ß, and –under endemic conditions, this would imply prevention of 0.08 infectious cases. This calculation assumes that the same relapse and failure rates apply to patients detected actively. In reality, cure rates may be expected to be somewhat lower.
For patients who would otherwise not report to the health services with symptoms, the effect is larger. Without active case finding, they would generate 2 ß infections. Those detected actively will now on average generate 1.2 ß infections (1 year would be the average duration of infectiousness at detection; the additonal 0.2 ß assumes similar failure and relapse rates as among self-reporting patients). Thus, in these patients transmission is reduced by 40% and 0.4 future infectious cases are prevented directly.
The impact of preventive therapy among HIV infected persons on transmission lies in the direct prevention of infectious tuberculosis cases. Smear-positive tuberculosis cases with HIV co-infection may be slightly less infectious than non-HIV-infected people but the difference is probably not large (46-48). If the life-time risk of those with TB-HIV co-infection to develop *infectious* tuberculosis is estimated at 25%, and a single 6 months course of INH preventive therapy would give a life-time protection of 25%, this single course would have prevented 0.06 infectious cases.

The impact of preventive therapy among children who are contacts of tuberculosis cases on transmission is estimated as follows. If the life-time risk of developing tuberculosis was 12% and the risk of developing infectious tuberculosis was 5%, then a six-months course of isoniazid with a protective efficacy of 60% would on average prevent 0.03 infectious cases. Among adults in the general population with latent infection the life-time risk to develop infectious tuberculosis due to reactivation may be in the order of 1.5% and preventive therapy would thus prevent approximately 0.01 infectious cases.

An overview of the estimated impact of tuberculosis control measures on avoiding infectious tuberculosis cases is shown in Figure 4.

Estimating short term population impact of case finding and treatment on transmission

It is clear that the effectiveness of the DOTS strategy at population level under the above assumptions depends on the case detection rate (i.e. the proportion of cases ever detected) and the cure rate (simplified here as: 1-failure rate). Using the same assumptions as above under varying case detection and cure rates, the resulting reduction in transmission in a given population is shown in Figure 5. An important implication of this analysis is that a programme with a cure rate of approximately 50% is expected to have no impact, and with a cure rate of less than 50% is expected to make the tuberculosis situation worse instead of better. As the latter programme would reduce mortality but not cure enough patients, the prevalence of infectious cases would increase. Diagnosis and treatment of smear-negative cases may - in comparison with the absence of control - lead to a similar proportional decrease in transmission given similar case detection and cure rates (Figure 5). However, as the number of infections per case is only 10-20% of that of smear-positive cases, the number

of infectious cases prevented as the result of treating one smear-negative case would be only 10-20% of that of treating one smear-positive case.

The effectiveness of active case finding depends not only on the case detection and cure rate of the tuberculosis programme in place, but also on the frequency of screening and the sensitivity of the screening method. For instance, if screening were done once in two years, only one sixth of patients otherwise detected through self-reporting have a chance of being detected actively (as the average delay period was assumed to be 4 months). With less frequent screening, the proportion of such patients detected actively will decline further. Figure 6 explores for a range of case detection and cure rates, what the additional percentage reduction in transmission would be under active case finding with different frequency and sensitivity. The options considered are screening every five years using a method with 90% sensitivity, screening every two years with a method with 70% sensitivity and annual screening with a method with 50% sensitivity. This shows that active case finding offers little benefit for transmission reduction as long as cure rates are below 70%. As might be expected, the largest benefit is observed when case detection rates are low. If case detection rates exceed 70%, the additional contribution of active case finding would be limited under the assumptions used, unless screening is possible at least annually and sensitivity is high. The frequency of screening appears to be very important. Similar impact can be obtained with less sensitive screening methods provided the frequency of screening is increased (Figure 6).

The impact of preventive therapy among HIV-infected people on overall transmission depends not only on the protective efficacy of the drug regimen, but also on the prevalence of HIV infection, the proportion of HIV infected people identified, the prevalence of tuberculosis infection among them, and the proportion of eligible patients completing treatment. The latter constraint was shown to be very important in Uganda, where HIV prevalence was high: of 9862 HIV-infected clients of voluntary counseling and testing

clinics, 5594 returned for their HIV result, 1344 were tuberculin skin tested, 520 received isoniazid, and 322 completed treatment (153).

Since of all infections generated by a source case, only those in children among close contacts may be identified, coverage of all those with recent infection is likely to be limited to perhaps 2-3 infected contacts on average per source case. Moreover, as this approach is labour-intensive, it is unlikely to be carried out for all infectious patients, thus further limiting coverage. Among adults with latent infection, treating one person only prevents 0.001 infectious cases. However, due to the large size of the target group, a substantial number of infectious cases could be averted if this intervention were applied at a large scale (3).

Cost-effectiveness estimates

There have been relatively few studies of the cost-effectiveness of TB control interventions in low and middle-income countries. Those that have been undertaken are summarized in Table 1, which for each study identifies the location, study date, main methods, key results and main reference. Most studies have focused on treatment for new smear-positive cases, and while implementation of the DOTS strategy is not usually explicitly identified as being one of the approaches to treatment evaluated, the short-course chemotherapy strategies considered do usually conform to the main principles of DOTS. Studies 1 through 4 (1,72,154-157) included comparisons with standard course chemotherapy, while those listed as 5 to 7 (41,42,158) involved comparisons of alternative approaches to delivery of short-course treatment. There is only one study that has attempted to assess the cost-effectiveness of BCG, and how this relates to treatment (159). There are no published studies regarding DOTS for smear-negative cases, though data from a recent WHO-coordinated project are due to be published soon. There is only one published study for active case finding (4), and also only one published study for prophylaxis for HIV+ individuals, which was based on data

from Uganda (127). There are no published studies concerned with the other interventions identified in Section 2 - namely preventive therapy among contacts, and preventive therapy for those with latent infection. As yet, there are no published studies on treatment for MDR-TB, though a study of the national standardized second-line drug treatment programme in Peru is due to be completed soon (160).

The best-known result is probably the finding used in the World Bank's World Development Report 1993, that short-course chemotherapy for new smear-positive patients costs US$1-3 per DALY (US$1-4 in 2000 prices). This result has often been used to argue that TB treatment is among the most cost-effective of all health interventions. Nonetheless, it needs to be borne in mind that the study was undertaken in some of the poorest countries in the world, where costs can be expected to be particularly low. It was also based on some of the best TB programme treatment outcome results achieved to date – many countries currently have poorer cure rates and higher death rates, especially where HIV prevalence is high. The figure of US$1-3 DALY may therefore be too low in some settings, especially middle-income countries where hospitalization for the "intensive phase" of treatment is common. The World Bank's World Development Report did estimate a range of US$5-7 per DALY in middle-income settings, but given that Study 6 in Table 1 found that the cost per patient treated can be around ten times higher than the costs per patient on which the US$1-3 figure was based, the cost per DALY could be around US$20-30 in middle-income countries. It may even be higher where HIV prevalence among TB patients is high, since this reduces the life years gained per patient treated - though it is still unlikely to be more than around US$40 per DALY (unpublished data, analysis available from KF). Meanwhile, short-course treatment – a key element of DOTS – has consistently been found to be more cost-effective than standard course chemotherapy, and the latter is now only rarely used.

The evidence on BCG is scanty, and the finding that its cost-effectiveness is similar to that of treatment for smear-positive cases in settings where the annual risk of infection is high (which is the case in most low and middle-income settings) should be treated with some caution. The result is based on the assumption of 50% efficacy for the BCG vaccine, 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 in 1986 prices (US$224 in 2000 prices) to add BCG to an existing immunization programme translates into a cost per DALY of less than US$10; even if BCG efficacy were much lower than 50%, it seems unlikely, on this basis, to have a cost per DALY above US$50.

When the cost-effectiveness of treatment of smear-negative cases with DOTS has been estimated for the same place and time period as for smear-positive cases (study 7, in Kenya and Malawi), the cost per DALY gained is about 2-4 times as poor for smear-negative cases (with both lower costs and lower effectiveness). This implies a cost per DALY of around US$10-20 in low-income settings, and, for reasons given above, possibly around US$100 in middle-income settings.

The only study concerned with active case finding suggests that it may be cost-effective in developing countries. This is based on estimation of threshold costs at which active case finding would have a cost per DALY of less than GNP per capita – a criterion chosen on the basis that societies should be willing to pay at least this amount to gain one DALY. Since these are threshold values, they cannot be directly compared with the values estimated for other interventions. Even so, since the cost per DALY for TB treatment is consistently well below per capita GNP, treatment of self-reporting cases does appear a more cost-effective intervention.

With only one study, it is also not possible to make definitive statements about the relative cost-effectiveness of prophylaxis for HIV+ individuals. In low-income countries, the use of isoniazid may have a cost-effectiveness ratio of below US$150 per DALY, but further research on costs and effects in practice rather than in theory are required – in particular to allow for compliance rates achieved.

The analysis for MDR-TB treatment in Peru is not yet finalized, and care is needed in comparing results with those for other interventions in low-income countries (as a middle-income country, non-drug inputs to care in Peru are generally higher cost and this needs to be accounted for when making comparisons). Within Peru, it is clear that costs are considerably higher and effectiveness considerably lower than treatment for new cases. The results suggest that this will also be the case in low-income countries. Cure rates for MDR-TB cases in Peru are generally lower than those being achieved by low-income countries for new cases, and drug costs alone for MDR-TB cases are higher than the cost of all inputs required for the treatment of new cases in low-income settings. Cost per DALY figures should be available in the near future.

Despite the limited evidence, these results indicate that DOTS for new smear-positive cases is probably the most cost-effective of the available interventions, followed by BCG, treatment of smear-negative cases, prophylaxis for HIV+ individuals, active case finding, and treatment for MDR-TB.

Two country examples: Tanzania and Vietnam

The potential contribution of intervention measures depends on the epidemiological situation in countries and the current implementation of control. For instance, if HIV is uncommon, preventive treatment of HIV infected people will contribute little to tuberculosis control.

Thus, the possible implications of these analyses for a national tuberculosis control programme are assessed below using two country examples: Tanzania and Vietnam. Tanzania and Vietnam belong to the 22 high-burden countries in which 80% of the world's tuberculosis cases are found and both have well-established DOTS programmes (6). For comparability, numbers for both countries were used as far as possible as published in a global overview of the tuberculosis disease burden (10), and where necessary data were not available, directly from the national control programmes.

Tanzania had an estimated incidence rate of smear-positive tuberculosis of 127 per 100,000, a case detection rate of 55%, a failure rate of approximately 10% (as deaths are removed as transmission sources, these are not considered failures from a transmission point of view; however, defaulters are considered programme failures), a tuberculosis infection prevalence of 40% among adults, and an HIV prevalence of 8% among adults. Vietnam had an estimated incidence rate of smear-positive tuberculosis of 85 per 100,000, a case detection rate of 82%, a failure rate of approximately 5%, a tuberculosis infection prevalence of 60% among adults, and an HIV prevalence of less than 0.5% among adults. For both countries we assumed that achievable coverage is 80% for active case finding, 5% for people with TB-HIV co-infection, 50% of 3 recently infected close contacts per infectious patient, and 80% for infected adults in a population survey. Treatment completion of preventive therapy was estimated at 60% for those with HIV infection and 50% for contacts and adults in the general population. The risk of progression from infection to infectious disease was estimated at 25% for those with HIV infection, 5% in contacts with recent infection, and 1.5% in adults in the general population. The contribution of various tuberculosis control measures in these two countries using these assumptions is summarised in Table 2. Numbers of cases prevented per 100,000 population in the short term by the current programmes are comparable: Tanzania has a higher incidence, but lower case detection and cure rates. In both countries, but more in Vietnam

than Tanzania, treatment of latent infection would make a substantial contribution to tuberculosis control. In Tanzania, active case finding might contribute importantly to tuberculosis control as would preventive therapy in people with TB-HIV co-infection. In Vietnam, these two interventions would have little impact on tuberculosis transmission, as the case detection rate is high and HIV prevalence is (still) low. However, in Vietnam some additional impact could be obtained by treating larger numbers of patients with smear-negative tuberculosis.

Discussion and conclusions regarding the effectiveness estimates

The estimates presented in this paper confirm that diagnosis and treatment of smear-positive tuberculosis patients is the most effective tuberculosis control measure available both for reducing mortality and for reducing transmission, and the promotion of its wider application should be strongly supported. However, additional tuberculosis control measures may be valuable, such as diagnosis and treatment of smear-negative tuberculosis, intensifying case finding of smear-positive tuberculosis in conditions where case detection rates are low, while cure rates are high; preventive therapy in HIV-infected individuals in HIV high prevalence countries; and perhaps treatment of latent infection in adults. Contact tracing, followed by preventive therapy in recently infected contacts, though beneficial for the individuals concerned, is likely to have very limited impact at the population level on tuberculosis incidence and mortality.

The parameters used to estimate effectiveness have several important sources of uncertainty, in particular those related to reducing transmission. First, their measurement is not straightforward. For instance, the duration of the infectious period and degree of infectiousness over this period is not well known and perhaps impossible to measure directly. Second, epidemiological parameters may vary among countries or over time within countries.

For instance, the effective contact rate in Europe has changed strongly over time probably in part due to changing social mixing patterns (64). Fortunately, many uncertainties (e.g. regarding the effective contact rate and risk of disease following infection) affect effectiveness estimates of different interventions in a similar way, having little effect on their relative effectiveness in terms of cases prevented.

Since the estimates of effectiveness suggest large differences between DOTS and the other intervention options, conclusions on the relative strength of DOTS are unlikely to be strongly influenced by uncertainties in the parameter estimates. However, it is clear that the estimated impact of all interventions provides a rough guide only, and further studies to estimate the impact of intervention programmes would be extremely helpful for decision making. When choosing intervention options in addition to DOTS, different choices may be made in different epidemiological settings, as suggested by the examples of Tanzania and Vietnam. As the differences in effectiveness between the additional options are not very pronounced, additional studies on the effectiveness of particular options in those settings are very much needed.

This study also has limitations related to its simple framework and the assumptions that were made. Although the simple framework has the advantage that it highlights the role of a few key determinants, it may have the disadvantage of ignoring potentially important variation (e.g. in diagnostic delay) and associations (e.g. between diagnostic delay and case detection rate). Moreover, although insight is given in the short-term impact of various control measures, only limited insight is given in the longer term impact. To overcome the latter limitation, a full dynamic transmission model may be needed (e.g. 2-4,16,17,56,57,64). However, as data related to potentially important variability and associations further discussed below are scarce, these uncertainties cannot be resolved easily and are faced by dynamic transmission models as well.

Estimates of the effectiveness of different case finding methods depend on the number of infections generated in three situations: (1) the absence of case detection, (2) case finding among self-reporting patients, and (3) active case finding. In the terminology above, this is captured as time. This may be oversimplified. For instance, the number of infections generated may initially increase with time since onset of symptoms (it may take some time before smear-positive disease has developed), but may later decrease, as most close contacts who are going to be infected at all may be infected early on. The former may lead to underestimating the effectiveness of case finding and treatment, the latter to overestimating it. The latter effect is likely to be the more important one.

The duration of the infectious period in the absence of treatment is uncertain, but may be longer than two years. If it were longer, the effectiveness of case finding and treatment were underestimated. This bias may partly counteract the above-mentioned bias, which led to overestimating the contribution of case detection and treatment.

If low rates of case detection were associated with longer patient delay, the effectiveness of case finding among self-reporting patients was overestimated for those situations and the additional contribution of active case finding underestimated. However, if such a bias has operated, this would strengthen the general conclusion that the contribution of active case finding is largest if case detection rates among self-reporting patients were low.

The number of cases prevented by case finding and treatment depends not only on the proportion reduction in transmission, but also on the average number of infectious cases generated directly by a single infectious case (i.e. the combination of transmission of infection and progression from infection to disease). The assumption that this effective reproduction number equals one should hold in stable endemic situations. This number could be somewhat more than one (leading to increasing incidence rates) or somewhat less than one (leading to declining incidence rates), leading to an underestimate and overestimate,

respectively, of the effectiveness of case finding and treatment. However, since case finding and treatment is so much more effective than the other interventions, this will not affect the priority order of the interventions.

Estimates of the short-term impact of preventive therapy were obtained more directly and their main sources of uncertainty appear related to implementation issues, such as coverage and compliance. To reduce this uncertainty, operational research would be needed to estimate these variables in various settings and using various approaches.

A limitation of our approach to compare the number of infectious cases prevented directly is that this effect occurs at different points in time for the different interventions. Preventive therapy in HIV infected individuals has an effect after on average approximately five years, while the effect of preventive therapy in those with latent infection may take on average ten to twenty years to materialise. The effects of reduced transmission through case finding and treatment and of preventive therapy in tuberculosis contacts depends on the serial interval and incubation period, respectively, and probably represents an intermediate situation. As early prevention prevents more secondary cases than later prevention, ignoring time will probably lead to an underestimate of the effect of preventive therapy in HIV infected people and to an overestimate of the effect in individuals with latent tuberculosis infection in comparison with the effectiveness of case finding and treatment.

Although relative effectiveness may be defined in relation to the short-term effect on transmission, long-term elimination requires that transmission be reduced to a fraction less than $(1/R_0)$, where R_0 is the basic reproduction number for that population. Unfortunately, estimating R_0 for tuberculosis is complicated and its interpretation is not straightforward (57). The further development of methods to allow its estimation would be of great help to national tuberculosis control programmes wishing to estimate the minimum amount of impact on transmission required to eliminate tuberculosis in the long term.

4. Constraints to scaling up diagnosis and treatment of smear-positive tuberculosis

Constraints to scaling up interventions are discussed in two sections: first constraints to scaling up DOTS, as this is the most effective intervention and attempts to scale it up have been made over the past decade. In the next section we will discuss constraints to scaling up the possible additional interventions.

WHO estimates that 23% of all smear-positive tuberculosis patients in 1999 were diagnosed within a DOTS programme (11). Although this represents considerable progress since 1995, when 11% were estimated to be diagnosed within a DOTS programme, major scaling up is still required. Possible reasons why DOTS is not applied on a larger scale are identified below.

Political will

The ad hoc committee on the tuberculosis epidemic of WHO suggested in London in 1998 that increased technical efforts would not be sufficient to bring about the required acceleration and expansion of the WHO strategy (161). The committee identified the following six principal constraints retarding action by health authorities: financial shortages, human resource problems, organisational factors, lack of a secure supply of quality anti-TB drugs, and public information gaps about the danger of tuberculosis (161). The committee stated that weak political will and commitment was the overriding constraint to improved global tuberculosis control. The following factors were considered important to get this political commitment and make it effective and sustainable:

- *popular perception* of tuberculosis as a priority problem with a real solution; increasing popular awareness would involve mass media use
- *technical consensus* on the role of the DOTS strategy, and

- *external concern* leading to international advocacy and support for tuberculosis control.

Since 1998 further developments have put tuberculosis higher on the international agenda. In the year 2000, a conference in Amsterdam involving Ministers of Health and of Finance of 20 of the 22 high burden countries countries as well as various international donors, endorsed the urgency of tuberculosis control and accepted responsibility for tackling it. This was followed up by discussions on a global DOTS expansion plan in Cairo in November 2000. Also in 2000, the G8 countries called for intensifying public health efforts against HIV, malaria, and tuberculosis aiming for a reduction of tuberculosis mortality by 50% over the next decade.

In countries that have reached the WHO targets of a 70% case detection and 85% cure rate, the major constraint is the sustainability of tuberculosis control over the next few decades (162). External financial support has been used to facilitate initial implementation and expansion. Unfortunately, the time scale of external support (typically five years or less) is much shorter than the time scale of tuberculosis control (decades). Gradual inclusion of the cost of tuberculosis control in the country's health budgets will be one of the important requirements for long term sustainability.

In countries where DOTS implementation is rapidly expanding, political will at the central level may not be matched by political will at lower (provincial, district) levels of government (162). Therefore, advocacy, capacity building, and supervision at peripheral levels appear key components in expanding tuberculosis control in these countries (162). In addition, special efforts may be required to have the DOTS strategy accepted by health professionals, as the criteria of quality used by clinical specialists are different from the public health criteria of quality of the DOTS strategy.

Organizational issues

In many high burden countries, private health care providers comprise an important part of the health system. While not-for-profit non-government organizations have been involved successfully in tuberculosis control, involvement of other private sector providers may be more difficult (163,164). Usually, case detection and cure rates in the private sector are unknown. While competition may offer a solution in some instances (attracting all tuberculosis patients to the public sector by providing a high-quality low-cost service), collaboration may be more promising in others. A systematic approach for public health programmes to make informed choices in this area appears not to be available.

Within the public health system, health sector reform is ongoing in many countries. This may provide opportunities to put tuberculosis control higher on the health agenda as it is an important public health problem with a very cost-effective solution (165-169). However, in some countries, health sector reform has led to weakening of tuberculosis control (170,171). This danger – not only for tuberculosis programmes, but for other infectious disease control programmes as well – may be present in particular if efforts to ensure integration and decentralisation ignore the technical requirements of infectious disease control programmes (170).

Ensuring access to anti-tuberculosis drugs is a key task of tuberculosis control programmes. Central ordering of drugs is used by many tuberculosis control programmes to obtain drugs at a reduced cost. A weakness of this system is that if anything goes wrong, for instance due to bureaucratic delays, large numbers of tuberculosis patients suffer. To prevent interruption of treatment, (important for keeping patients' confidence and to prevent drug resistance) patient-wise boxes have been found to be helpful, for instance in India and Peru: a box of drugs is reserved for each patient at the onset of treatment (172). To ensure rapid access to low cost drugs, and to provide drugs in emergency situations, a global drug facility might help.

Technical issues

Sputum smear microscopy is labour-intensive and requires trained laboratory staff, functioning microscopes and a system for quality control. Further, its sensitivity is limited. Although these constraints can be overcome, new diagnostic tools, which would simplify case finding, would be very helpful in support of the DOTS strategy. Other important technical constraints concern the duration of treatment (6 to 8 months) and the required frequency of contact with the health worker. With the use of currently available technology, it is important to try and identify ways of simplifying treatment delivery while ensuring high cure rates. This is closely related to the issue of identifying determinants of programme success (90). For instance, why did both DOT and non-DOT have a low cure rate in a study in South Africa (84) and Pakistan (92), and why is another programme with only weekly DOT so successful (89)? Another solution to constraints related to the frequency and duration of treatment may lie in the development of new drugs, or perhaps by developing new treatment methods (such as long-acting preparations) on the basis of currently available drugs.

Another option to simplify treatment delivery is that of fixed-dose combination tablets (173). Although these do not reduce the frequency of taking drugs or the duration of treatment, they simplify taking the drugs and prevent treatment by single drugs. They might reduce defaulting, if this were due to the perception of patients of side effects being due to the bulk of the separate tablets. However, fixed-dose combination tablets need to be of high quality to ensure, in particular, a sufficient bioavailability of rifampicin. Another concern may be a reduced shelf-life.

5. Constraints to scaling up other interventions

If the constraints for case finding and treatment of patients with smear-positive tuberculosis can be overcome, this would facilitate the diagnosis and treatment of smear-negative cases as well. However, an additional constraint for smear-negative tuberculosis is the difficulty of diagnosis, due to the limited specificity of chest X-ray and in HIV-infected people also its limited sensitivity. Over-treatment for smear-negative tuberculosis drains resources (both drugs and costs of follow-up) and may affect the perceived success of the programme, as patients with diseases other than tuberculosis may not be cured by tuberculosis drugs. Additional tools for diagnosing smear-negative tuberculosis would therefore be extremely helpful. Reducing the duration of treatment would be extremely helpful as well, although this may not be possible with currently available drugs (174).

Although active case finding may seem promising for programmes with high cure rates and low case detection rates, it is uncertain whether it is cost-effective. Before embarking on this, a number of questions need to be answered: Why are case detection rates low, while treatment performance is good? Is the cause of low case detection limited accessibility of health services? Are services reached, but is the diagnostic performance low? Is it possible to increase the accessibility or attractiveness of the services? What happens to patients not detected? Are they served by the private sector? If so, what is the technical performance of the private sector? In short, is active case finding indicated, or do other options to increase access to tuberculosis diagnosis appear more promising?

If active case finding is considered an attractive option, further questions need answers. Although diagnosis on a mass scale will be a major effort, an even larger effort is implied in the treatment of those found to have tuberculosis. The rate of defaulting may be higher in patients detected actively, and special efforts may be required to motivate patients and to organise follow-up for defaulters. In particular if low case detection rates are the result of

inaccessible services, outreach programmes to diagnose more cases only make sense if accompanied by outreach programmes to treat the cases detected. Also, it needs to be determined whether the total cost is affordable. If active case finding is expected to be feasible, it would be advisable to try it out in one or two districts before scaling up to national level.

An area of active case finding not included in the effectiveness estimates above is that among special risk groups such as prisoners, refugees, and the homeless. If active case finding is not indicated in general population, for instance because the case detection rate is acceptable overall, it may be indicated among such risk groups, in particular if there are reasons to believe that tuberculosis prevalence is high or if access to tuberculosis treatment is limited. Special surveys among these risk groups may show whether this is indeed the case.

Preventive therapy in HIV infected individuals with tuberculosis co-infection 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 of people with TB-HIV co-infection and in ensuring compliance with preventive therapy. Although the identification of people with HIV infection is relatively easy among HIV-infected tuberculosis patients having completed treatment (135), it may be much more difficult for individuals with early, asymptomatic, HIV infection. Intitiatives in voluntary counseling and testing (such as the Pro-Test initiative (175)) will be important to help solve these practical problems. It is clear that HIV and tuberculosis programmes will need to work together to develop successful approaches in ensuring patient compliance.

Preventive therapy in contacts is unlikely in most settings to achieve sufficient coverage to have an impact on tuberculosis transmission. Therefore, scaling up this intervention appears not to be a priority.

Major constraints for preventive therapy among adults with latent infection in the general population include the following: (1) Detecting infection is complicated (3 days between giving skin test and reading it). As a total population survey seems indicated, a simpler test would be very helpful. (2) Interpretation of the tuberculin skin test may be difficult in tropical countries (cross-reactions due to infections with environmental mycobacteria are common). However, as adults in endemic countries have a high prevalence of tuberculosis infection, the positive predictive value of the test is expected to be high; (3) Most importantly, compliance with preventive therapy is likely to be low. Large scale preventive therapy would be much more likely to be successful if drug administration can be simplified. Moreover, are side effects such as lethal hepatitis due to isoniazid rare enough to make large scale application politically acceptable? A rate of 1 per 10,000 may seem low (176), but if millions of people are treated, hundreds may die. This may pose serious problems, even if the risk of dying from tuberculosis in the absence of preventive therapy were higher. Thus, new drugs to be developed would need to be simpler in administration (ideally a single shot), but also have an extremely low risk of severe side effects.

Another potentially useful approach for research would be to identify risk factors for progression from infection to disease. If it were possible to identify those with a high risk of disease progression, directly observed, short course preventive therapy for this group would be a very promising strategy. To date, no strong risk factors have been identified yet, with the exception of HIV infection.

Constraints in implementation of large scale BCG vaccination have been taken care of by the Universal Childhood Immunization initiative. For tuberculosis control the problem of BCG vaccination is not its scale of application, but the low protective efficacy against smear-positive tuberculosis in adults. Recent advances in research, including the sequencing of the

genome of *M. tuberculosis,* have raised hopes that better, new vaccines may become available over the next few decades (177,178). This paper re-emphasises the need for a new vaccine with a high protective efficacy against smear-positive tuberculosis in adults.

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Table 1. Summary of cost-effectiveness studies of TB interventions.

Intervention	Place, date of study	Main methods	Key Results	Ref.
DOTS, new smear-positive cases	1. Malawi, Mozambique, Tanzania, 1991	1. Analysis of cost data from 1988/9; empirical treatment outcome data from 1980s; epidemiological model used to assess secondary deaths averted through prevented transmission	1. Cost per DALY US$1-3 for short-course chemotherapy, which is more cost-effective than standard course chemotherapy	1,69, 150a
	2.-4. Botswana, 1986; Thailand, 1992; Indonesia, 1989	2.-4. Analysis of empirical cost and effectiveness data	2.-4. Short-course chemotherapy more cost-effective than standard course chemotherapy	150b ,c,d
	5. Uganda, 1995	5. Used empirical cost data; empirical effectiveness data for existing care strategy (hospitalization in intensive phase), assumptions about effectiveness for ambulatory care	5. Ambulatory care with strengthened supervision likely to be more cost-effective than hospital-based care	150e
	6. South Africa, 1997	6. Analysis of empirical cost and treatment outcome data	6. Community-based care more cost-effective than 3 other health-facility based approaches to care, including that widely used in rural Africa	40a 40b 76
	7. Botswana, Kenya, Malawi, South Africa, Uganda (1997-2000, currently being prepared for publication)	7. Analysis of empirical cost and treatment outcome data for (a) conventional health facility-based approaches to care and (b) increased decentralization and involvement of communities in provision of care	7. Pilot approaches involving decentralization and community-based care almost always more cost-effective than conventional health-facility based care	

Table 1 (Cont'd). Summary of cost-effectiveness studies of TB interventions.

BCG	1. Developing countries, 1990	1. Estimates of both costs and effectiveness based on existing studies, in particular Tanzania, Botswana and Indonesia	1. Cost-effectiveness may be similar to that of treatment at high ARI, poorer at low ARI. Cost per death averted US$144 in 1986 prices in Botswana when BCG is added to existing immunization programme	150 f
DOTS, new smear-negative cases	1. No published studies, data currently being prepared for publication for Malawi and Kenya as part of WHO-coordinated "Community Care for TB in Africa" project (listed as 7. above)	1. Data currently being analysed based on empirical cost and treatment outcome data collected 1997-1999. Estimates of cost per DALY made, based on similar assumptions to those used in study 1. listed above but with appropriate adjustments for lower infectiousness of cases, higher rates of false positive diagnosis, and high rates of HIV infection	1. Cost-effectiveness of treatment for smear-negative cases about 2-4 times poorer than treatment for sm+ cases	
Active case finding	1. Major geographical regions (as defined by the World Bank), 1998	1. Estimation of threshold costs at which ACF strategies would have a cost per DALY below per capita GNP	1. ACF may be cost-effective in low and middle income countries in e.g. Asia, Sub-Saharan Africa	4
Preventive therapy in HIV+ adults	1. Uganda, 1999	1. Cost data from other studies (number 5 above); effectiveness modelled using efficacy data and estimates of secondary infections caused per TB case from elsewhere	1. Cost per QALY US$114-260 if medical costs only considered	124
Interventions to address MDR-TB	1. Peru, 2001	1. Analysis of empirical treatment outcome data for a cohort of 466 patients treated 1997-1999; analysis of empirical cost data. Possibly modelling to incorporate impact on transmission	1. Analyses still underway but cost per DALY clearly much higher than for treatment of new cases	150 g

Table 2. Expected impact of various tuberculosis control measures on mortality and transmission in Tanzania and Vietnam.

Strategy	Total number of tuberculosis deaths prevented directly per 100,000 population per year		Total number of infectious cases prevented directly per 100,000 population per year	
Current programme	Tanzania	Vietnam	Tanzania	Vietnam
Treatment smear+, self-reporting	35.0	34.9	46.1	50.9
Treatment smear-, self-reporting:	7.7	3.2	5.1	2.3
Total current programme	**42.6**	**38.0**	**51.2**	**53.2**
Additional options to consider				
Allow more smear-negative cases on treatment	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+/TB+ to be captured+complete Rx	3.6	0.3	7.2	0.5
Contacts	0.2	0.2	1.6	1.6
Adults general population	0.2	0.3	3.6	6.5

Assumptions:

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.

Vietnam: incidence 85/100,000, case detection rate 82%, failure rate 5%, infection prevalence among adults 60% for tuberculosis and <0.5% for HIV.

Both: achievable coverage: of active case finding among adult population 80%, of HIV-infected 5%, of contacts 50%, and of adults with latent infection 80%; 3 child household contacts per infectious case; treatment completion of preventive therapy 60% among HIV-infected and 50% among contacts and adults in general population; risk of progression from

infection to infectious disease 25% among HIV infected, 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 Figures 4-6.

Figure 1. Estimated tuberculosis incidence rates, 1997 (Source: Communicable Diseases Surveillance, World Health Organization).

Figure 2. Estimated number of tuberculosis case numbers in 1997 (Source: Communicable Diseases Surveillance, World Health Organization).

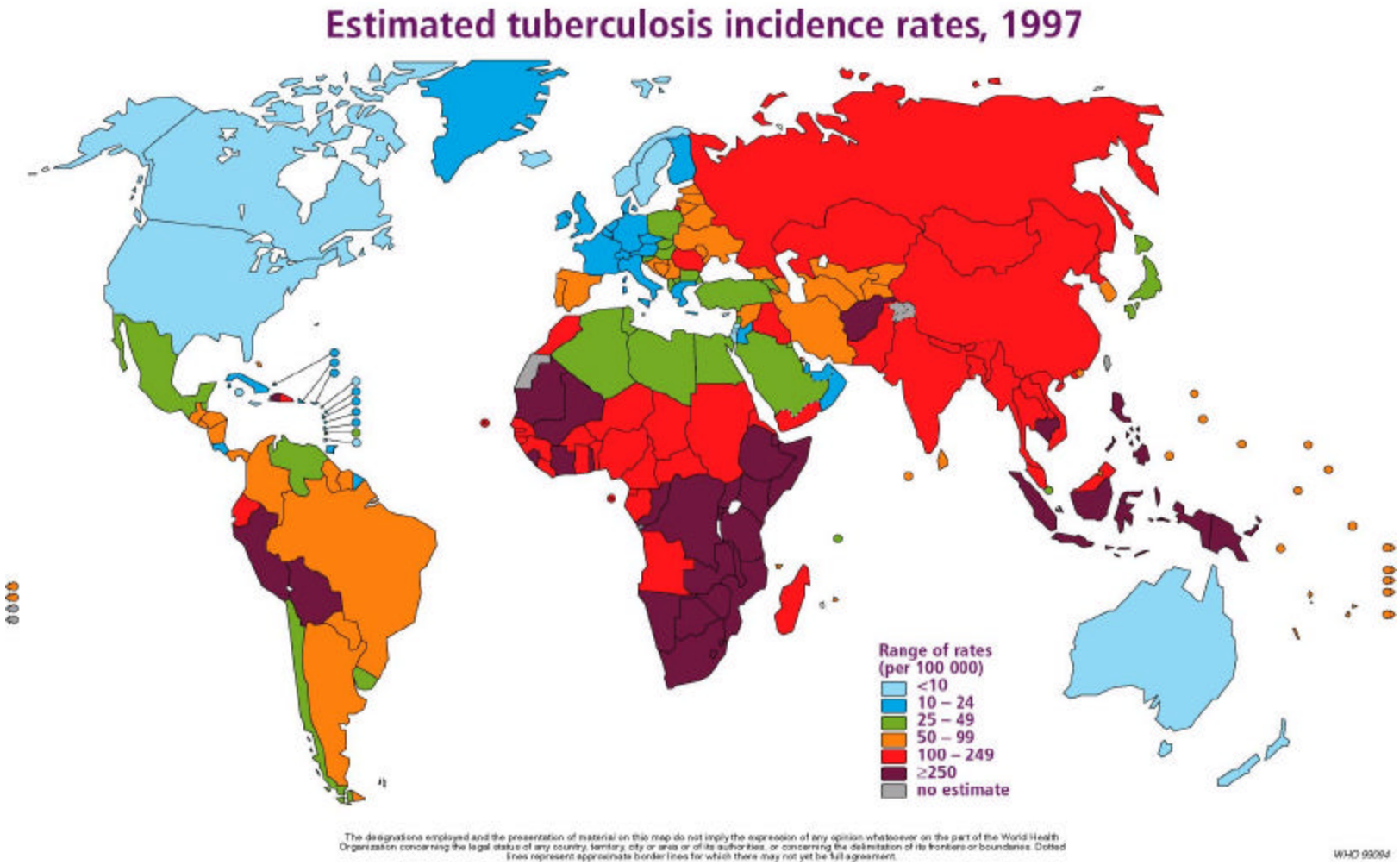
Figure 3. Number of deaths avoided when treating a single case.

Figure 4. Number of future infectious cases avoided directly when treating a single case

Note Figure 4: For treatment of smear-positive and smear-negative tuberculosis the number of future cases avoided is estimated using the assumption that each smear-positive case would in the absence of treatment generate one smear-positive case. In those receiving preventive therapy, the infectious cases avoided directly would have occurred in those taking prophylaxis.

Figure 5. Reduction of tuberculosis transmission as a result of treatment of patients self-reporting to health facilities under various programme conditions.

Figure 6. Additional reduction of tuberculosis transmission due to active case finding under various programme conditions with regard to patients self-reporting to health facilities.


Estimated tuberculosis incidence rates, 1997
Range of rates
(per 100 000)
<10
10 – 24
25 – 49
50 – 99
100 – 249
≥250
no estimate
The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines represent approximate border lines for which there may not yet be full agreement.
WHO 99094

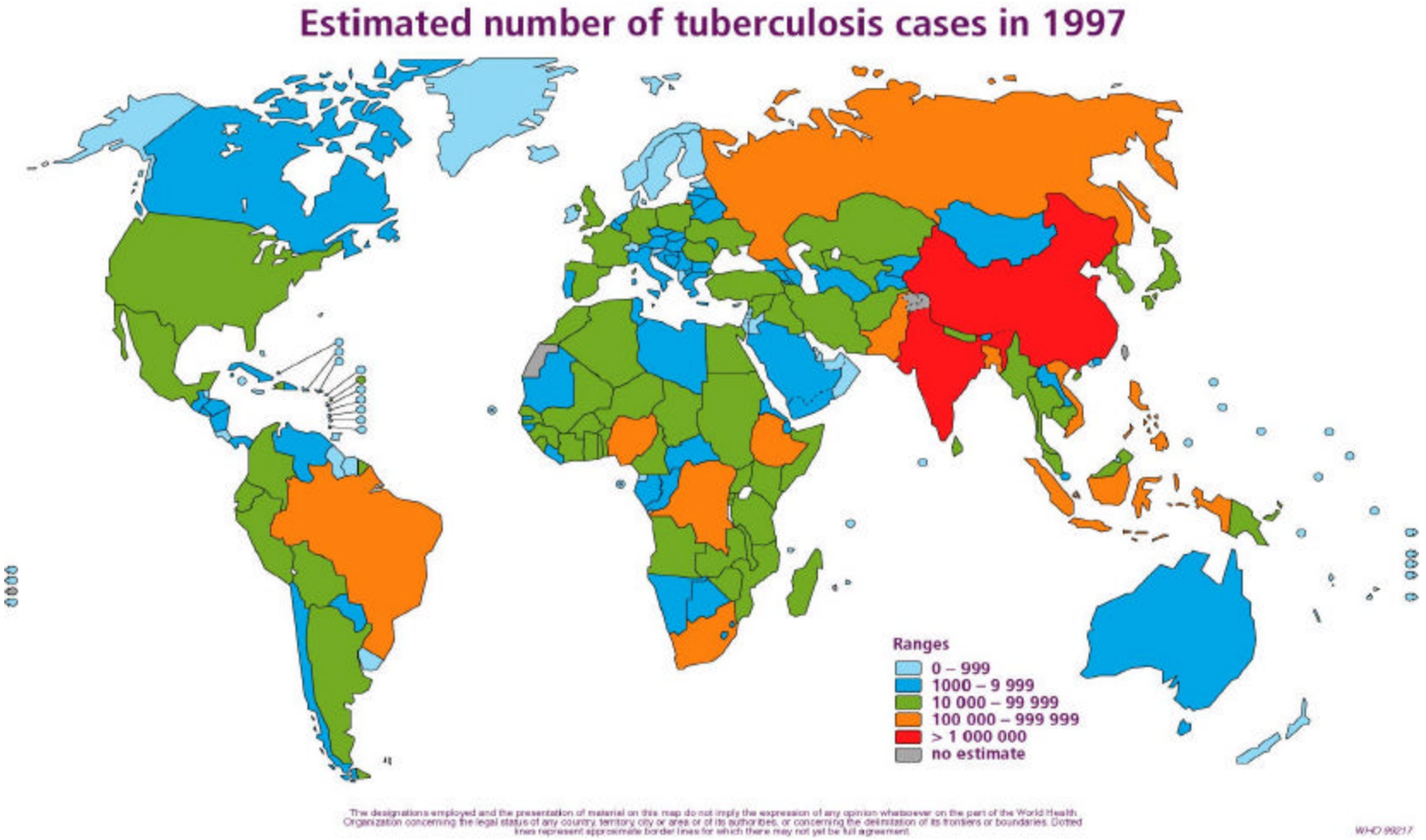

Estimated number of tuberculosis cases in 1997
Ranges
0 – 999
1000 – 9 999
10 000 – 99 999
100 000 – 999 999
> 1 000 000
no estimate
The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines represent approximate border lines for which there may not yet be full agreement.
WHO 99217

Figure 3

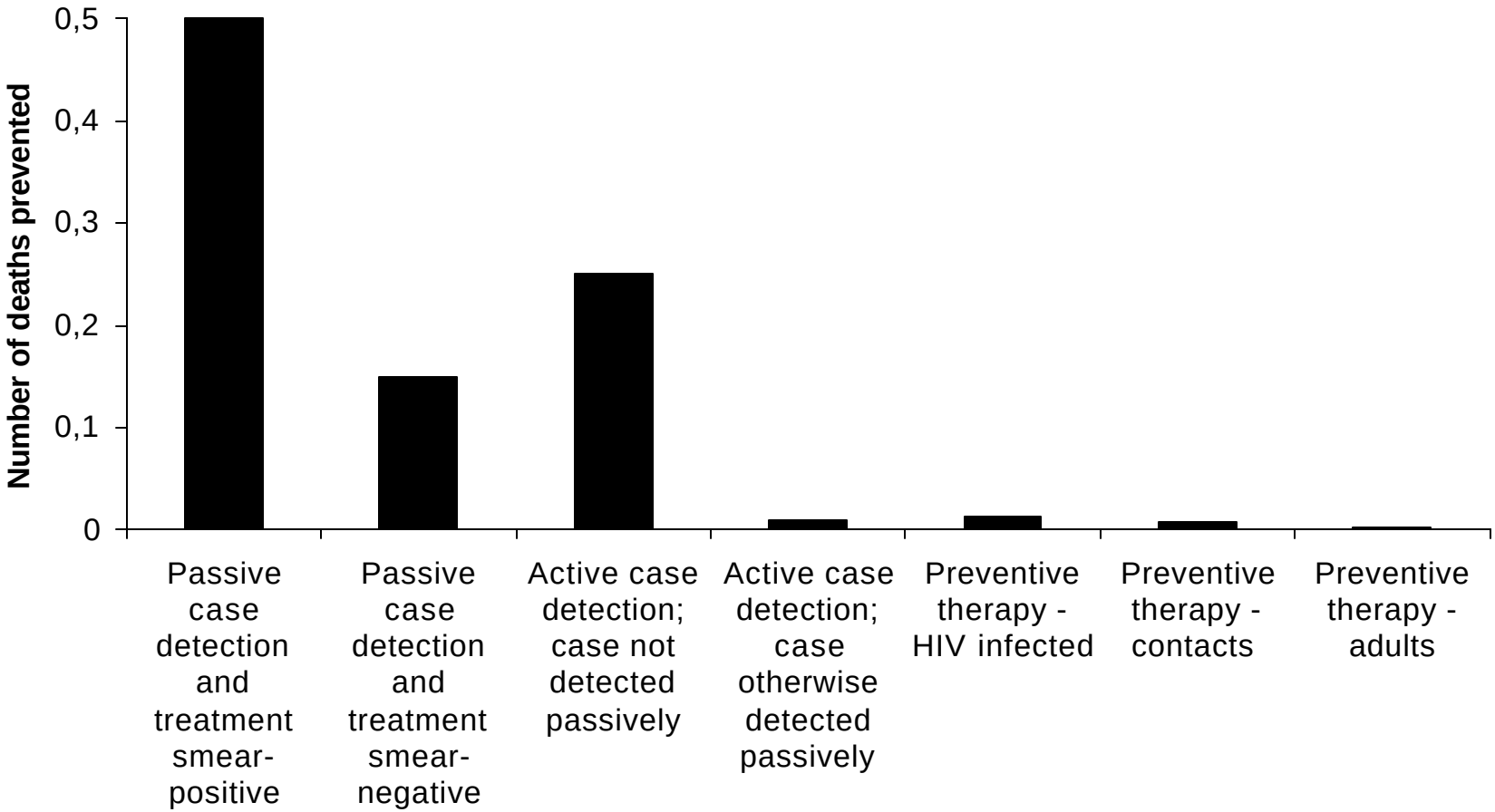

Number of deaths prevented
0,5
0,4
0,3
0,2
0,1
0
Passive case detection and treatment smear-positive
Passive case detection and treatment smear-negative
Active case detection; case not detected passively
Active case detection; case otherwise detected passively
Preventive therapy - HIV infected
Preventive therapy - contacts
Preventive therapy - adults

Figure 4

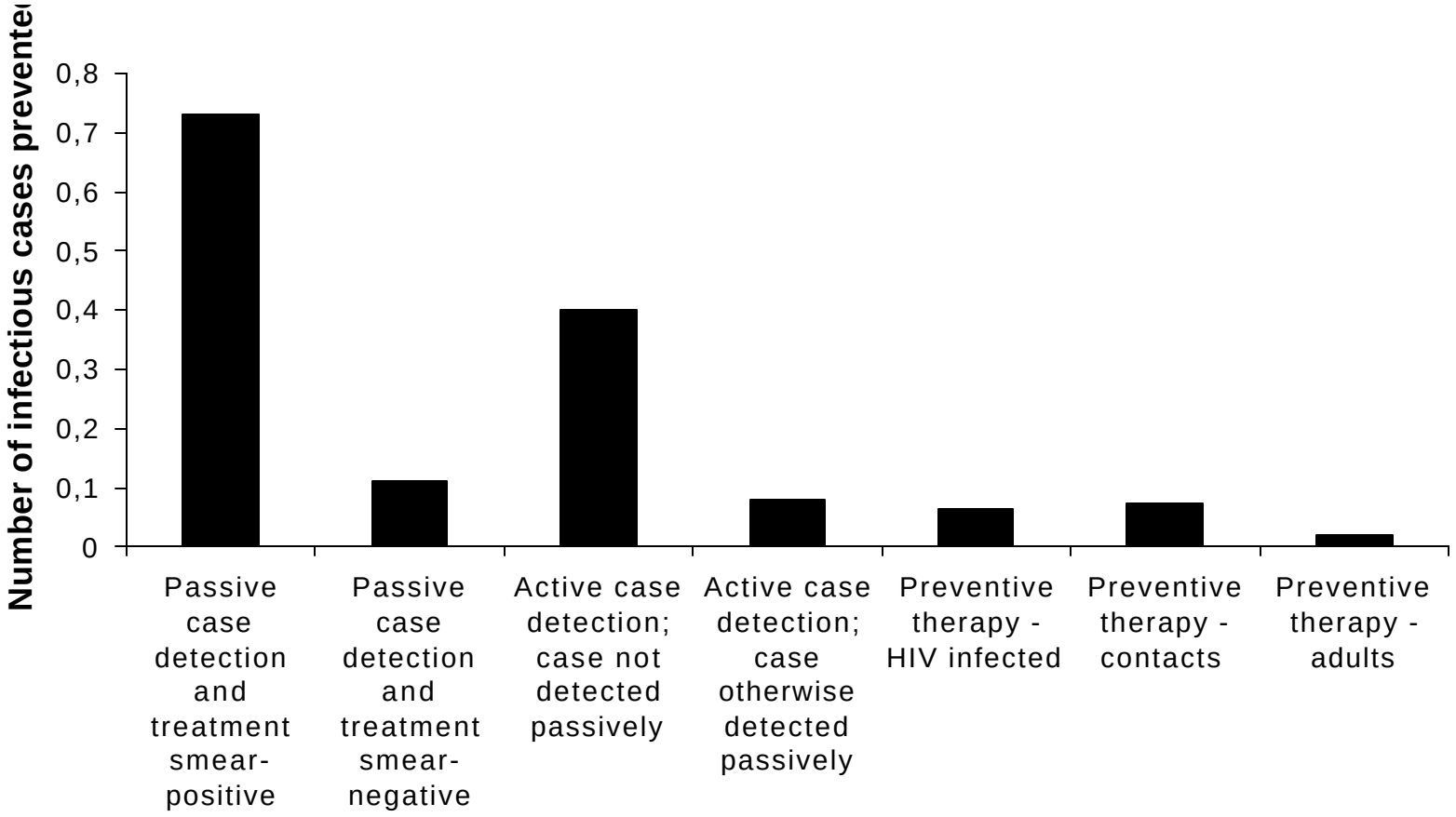

Number of infectious cases preventel
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
Passive case detection and treatment smear-positive
Passive case detection and treatment smear-negative
Active case detection; case not detected passively
Active case detection; case otherwise detected passively
Preventive therapy - HIV infected
Preventive therapy - contacts
Preventive therapy - adults

Figure 5

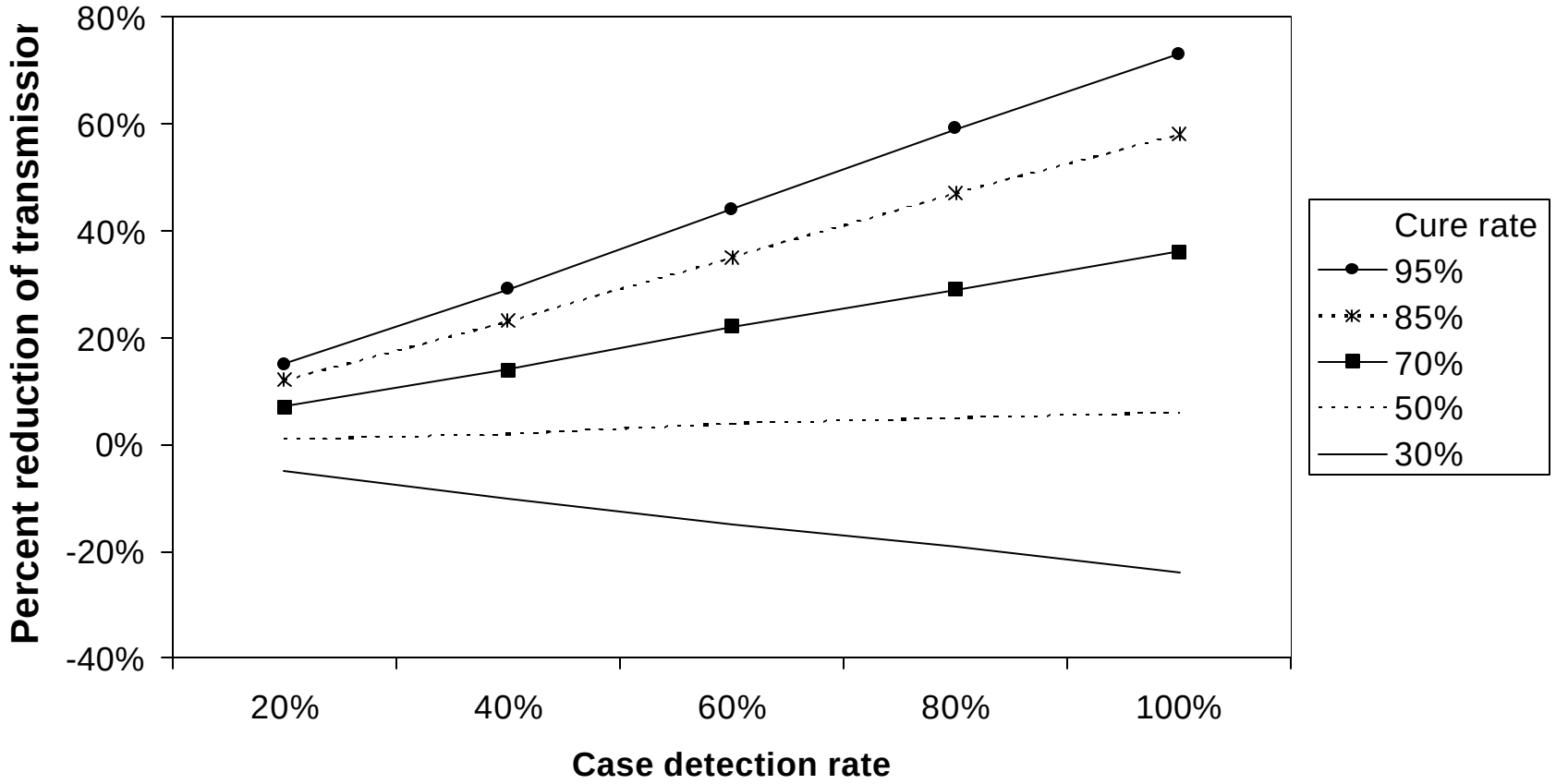

Percent reduction of transmissior
80%
60%
40%
20%
0%
-20%
-40%
20%
40%
60%
80%
100%
Case detection rate
Cure rate
95%
85%
70%
50%
30%

Figure 6a

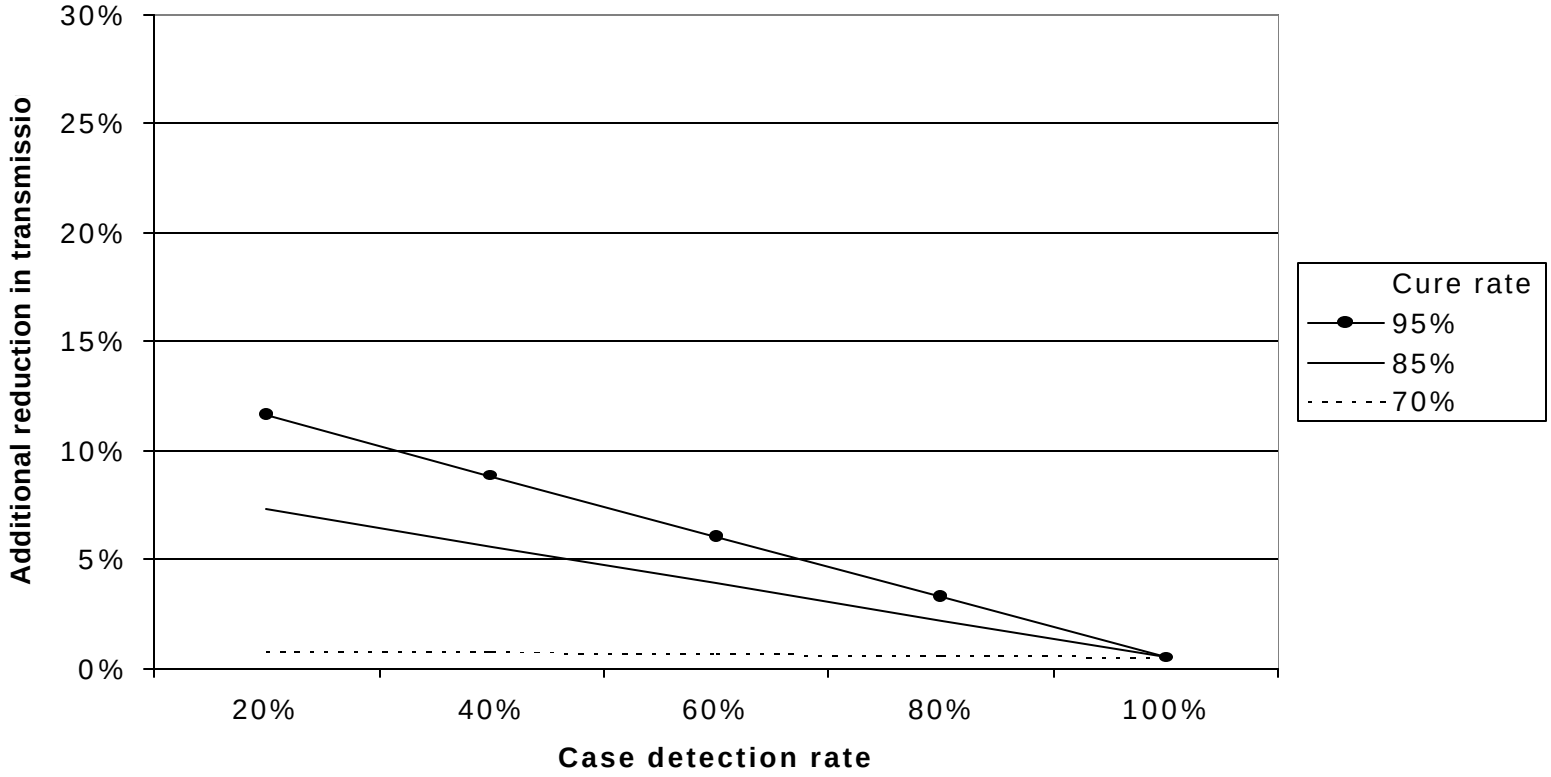

30%
25%
20%
15%
10%
5%
0%
Additional reduction in transmissio
20%
40%
60%
80%
100%
Case detection rate
Cure rate
95%
85%
70%

Figure 6b

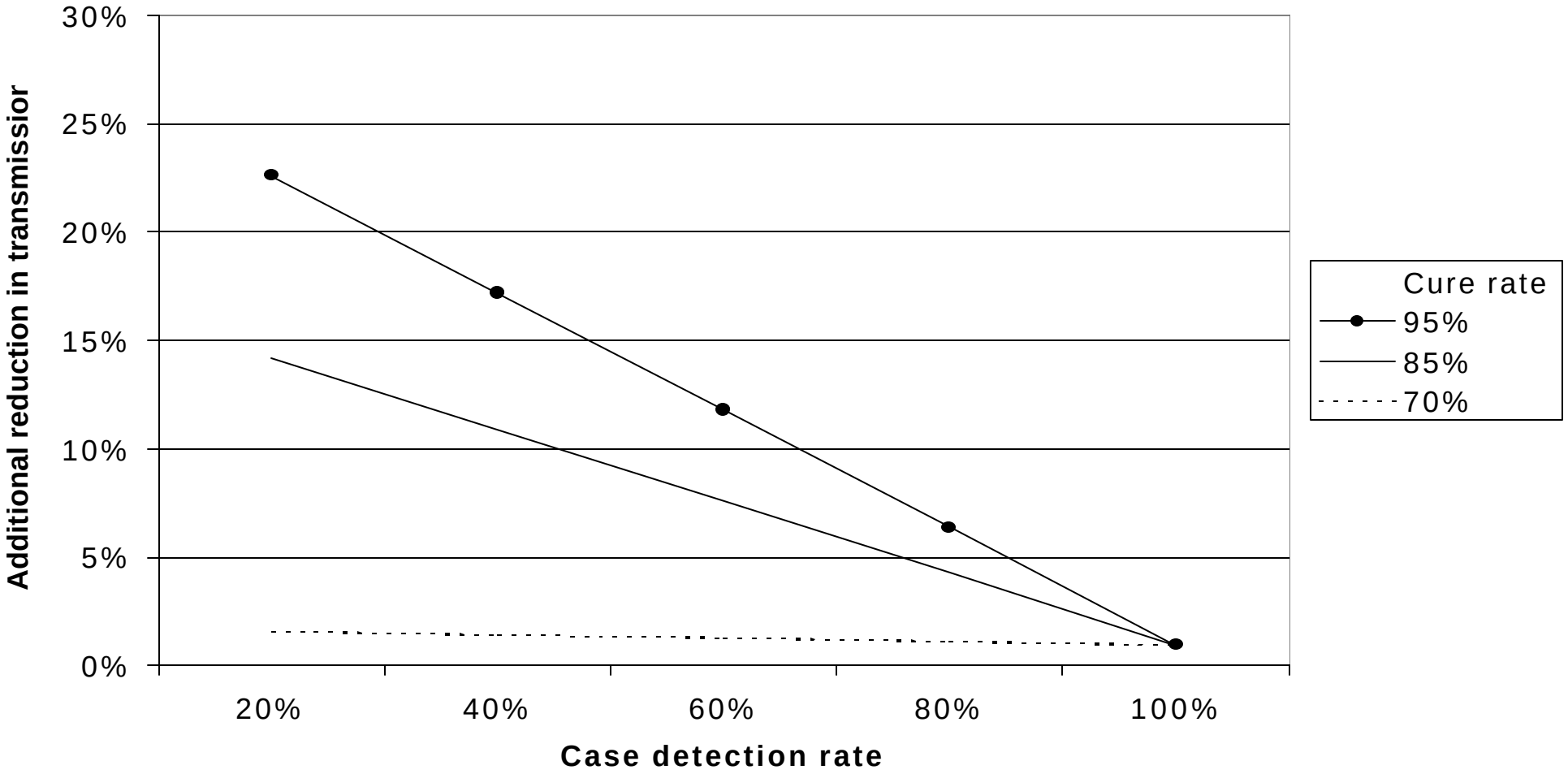
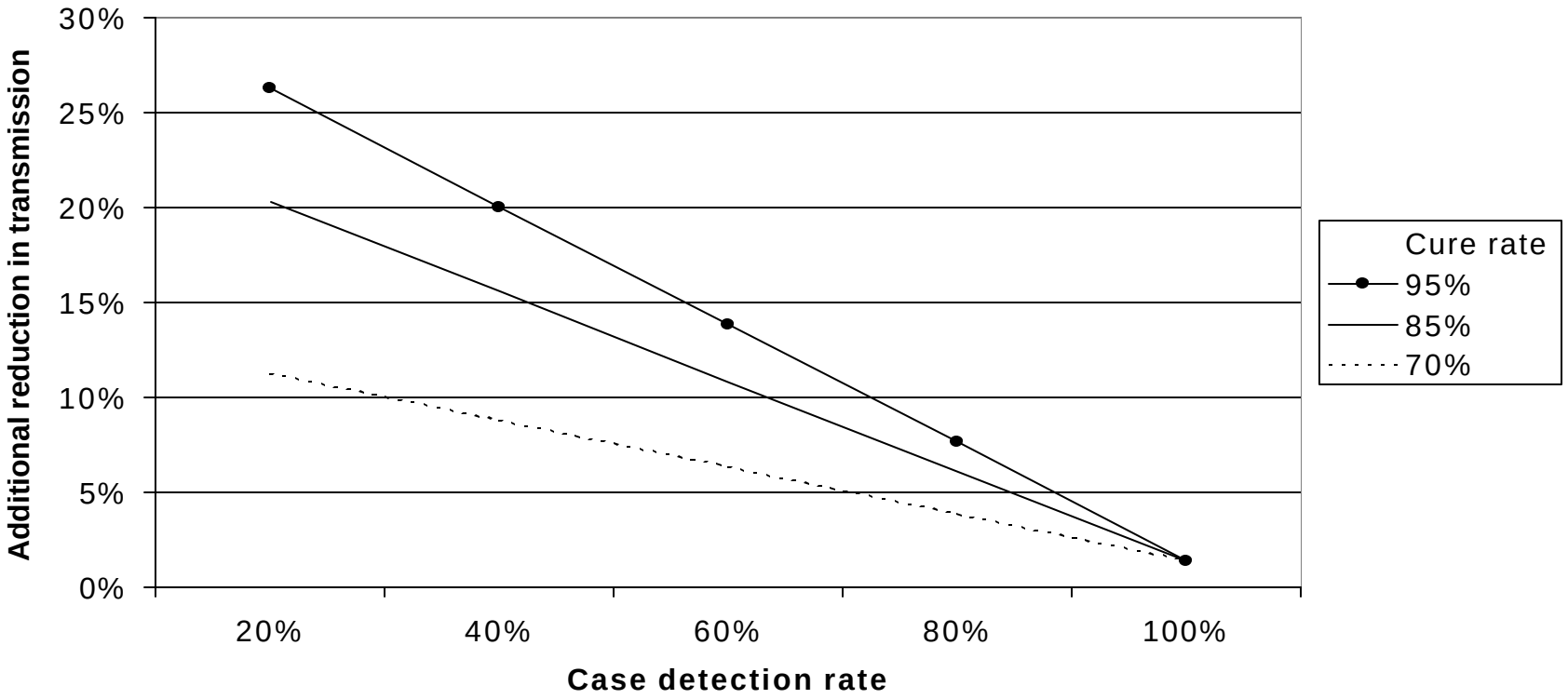

30%
25%
20%
15%
10%
5%
0%
Additional reduction in transmissior
20%
40%
60%
80%
100%
Case detection rate
Cure rate
95%
85%
70%

Figure 6c


Additional reduction in transmission
30%
25%
20%
15%
10%
5%
0%
20%
40%
60%
80%
100%
Case detection rate
Cure rate
95%
85%
70%