The costs and cost-effectiveness of tuberculosis control

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Citation for published version (APA):

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Chapter 1

General Introduction
INTRODUCTION

Tuberculosis (TB) is a principal cause of mortality and morbidity among the adult population of low income countries. The Commission on Macroeconomics and Health (CMH) reports that TB contributes substantially to the avoidable mortality of the world’s poorest. The World Health Organisation (WHO) recommended strategy for TB control is known as DOTS (Directly Observed Treatment, short-course). DOTS is based upon the premise that the early detection and effective treatment of TB cases reduces both the current burden of TB and the spread of the disease. This strategy has been proven to be highly effective and cost-effective in low income settings (1). However, today DOTS is only available to around half the world’s population and thus there remains a considerable mountain to climb to ensure global access to effective TB treatment. In March 2000, governments from around the world formalised the accelerated expansion of DOTS in the Amsterdam Declaration to Stop TB. The Global Stop TB partnership has built on this commitment and developed a plan of action, the Global Plan for TB Control. This was further updated to the Global Plan II for 2006-2015, in line with the Millennium Development Goals. A central aim of the plan is to ensure that by 2015 70% of notified TB cases globally will have access to DOTS.

The pursuit of global access to DOTS faces significant challenges as the TB epidemic is constantly evolving. If TB control is to be successful, DOTS will need to be adapted and extended to face these challenges. The foremost challenge faced is co-infection between TB and HIV/AIDS. This is rapidly increasing the severity of the TB epidemic, particularly in Sub-Saharan Africa. In addition, the emergence of multi-drug resistance TB (MDR-TB) threatens to limit the effectiveness of TB treatment for current and future generations. Finally, TB control faces a significant challenge in trying to reach the poorest of the poor, a group that is highly susceptible to TB. Although these challenges are considerable, there are opportunities ahead. Developments in health systems and new diagnostic tools, drugs and vaccines all have an important contribution to make to the effectiveness of TB control in the future.

Improving the evidence base on the economic and financial aspects of TB control can contribute towards TB control in the following ways:

Firstly, economic analysis can be used to justify domestic and international investment in TB control. If TB control is to meet the challenges it faces it will require both innovative approaches and increased resources. Economic analysis provides policy-makers and planners with a clear framework to justify investment in TB control compared to investment in other areas. In particular, it can be used to justify the use of public finances for TB control by assessing market failure and identifying efficiency gains.
Secondly, economic analysis can assist policy makers and planners identify the interventions that best achieve TB control objectives, given the available resources, by comparing the cost-effectiveness of different interventions. It is particularly useful in low income countries where the burden of TB is the highest, but resource constraints most severe. Economic analysis also has a role to play in the development of the extensions to DOTS required to meet the challenges of HIV/AIDS, MDR-TB and poverty. Through the assessment of the potential markets and cost-effectiveness of new prevention, diagnostic and treatment technologies, economic analysis can support investment in the development of new technologies to control TB.

Thirdly, financial and economic analyses have a role to play in supporting TB policy makers, planners and managers identify, plan and channel financial resources to and within TB control programmes. Economic analysis provides a framework to examine the resource gaps which exist, estimate the resource requirements of filling them and to develop the most efficient ways to finance them. The development and use of improved tools for the estimating resource requirements and the financial planning of TB control are essential to support the successful implementation of TB control programmes.

This thesis aims to contribute towards this effort by improving the evidence base on the costs and cost-effectiveness of a variety of TB control interventions.

BACKGROUND AND LITERATURE REVIEW

This section summarises the evidence on the costs and cost-effectiveness of TB control interventions available prior to conducting this thesis. It begins by looking at the cost-effectiveness of TB Control and DOTS generally and the evidence base for their comparative cost-effectiveness in low income countries.

This summary contains a detailed examination of the evidence establishing the cost-effectiveness of different elements of DOTS compared to their alternatives. It first examines the cost-effectiveness of different methods of case detection and evidence of the relative cost-effectiveness of passive approaches. It moves on to look at the cost-effectiveness of different ways of diagnosing TB and in particular the evidence that established the cost-effectiveness of smear microscopy. Finally, evidence of the cost-effectiveness of short course standardised therapy and improving treatment compliance are examined. The last part of this summary looks at the cost-effectiveness of extensions/ new additions to DOTS, including evidence on the treatment of MDR-TB and interventions to reduce TB related to HIV.
**Directly Observed Treatment Strategy (DOTS)**

The World Development Report 1993 (WDR 1993) identifies the detection and treatment of TB as one of the most cost-effective health interventions. It estimates that the cost per DALY of treating a smear positive case of TB is $1-3 (1993 prices) and therefore recommends its inclusion in the essential package of health care for both low and middle-income countries. In addition, it is estimated that the cost of diagnosis and treatment of smear negative TB is likely to be in the range of $5 to $20 per DALY (2), still a comparatively cost-effective intervention. The main source of data for the estimates used in the WDR 1993 is a study of the cost-effectiveness of TB control conducted in Malawi, Tanzania and Mozambique in 1991 (3). This study clearly demonstrates that in all three countries TB control is a cost-effective intervention. One of the main reasons for this finding is that, although TB treatment is often thought to be a curative intervention, its main benefit is preventative and therefore compares favorably against most other interventions, despite the relative expense and long course of treatment.

There are several studies that focus on measuring the gains in cost-effectiveness made from moving from existing systems of TB control to DOTS. This type of study often supports the re-orientation of substantial TB infrastructure away from hospitalisation towards integrated ambulatory care. A study from South Africa (4) finds that cure rates rose substantially when TB treatment was provided through twice weekly ambulatory care with a 2-3 week initial stay in hospital, compared to hospitalisation for the whole course of treatment, making it substantially more cost-effective. Furthermore a study from Uganda, also shows that the cost-effectiveness of TB control is likely to increase as patients are moved from hospitalised care to ambulatory DOT(5).

In recent years, this issue has become increasing relevant in middle income settings, where a TB control infrastructure is well established, but TB remains a threat. Cost-effectiveness studies can demonstrate the economic gains of adopting DOTS to policy makers who may be reluctant to apply evidence solely from low-income settings. For example, studies from Russia show that moving from a TB control strategy based on active case detection and individual hospitalised treatment to one based on passive case finding and ambulatory short course therapy significantly improves cost-effectiveness (6,7). Nevertheless more examples are still required to demonstrate that DOTS is cost-effective in middle-income countries.

**Elements of DOTS**

Whilst the DOTS strategy overall is seen as being cost-effective, different elements of the strategy have also been subjected to economic evaluation, in order to inform its design.
Case detection
The WHO recommends passive case detection, that is, case finding among symptomatic patients self-reporting to health services. The alternative, active case detection, involves screening populations using chest X-ray, or by surveying respiratory symptoms. There are no recent cost-effectiveness studies in low-income countries. However, one of the studies from Russia, which has a history of using active case detection, shows that it is less cost-effective (7). The cost of a case detected through active methods is estimated to be up to five or six times the cost of a passively detected case. In addition the conclusion that passive finding is more cost-effective than active case finding is intuitive, given the widespread experience that improvements in diagnostic services lead to substantial increases in the notification of TB cases, but have a considerably lower cost than providing screening detection. Sputum–positive TB is highly symptomatic and surveys show that high proportions of patients seek care relatively quickly if high quality and low cost diagnostic and treatment services are available. In addition, clinical TB develops quicker than the shortest possible screening intervals, and therefore screening does not always detect cases before they become infectious.

The finding that passive case detection is more cost-effective than active screening does not mean that active screening should not be provided. It only implies that passive screening should be established first. In some circumstances active screening for TB may still be cost-effective compared to other health interventions. At the current time, case detection methods are coming under renewed scrutiny as, despite the fact that some countries have good laboratory services, high DOTS coverage and cure rates, many of them still have low case detection rates. In these circumstances, where capacity has been developed to provide effective passive case detection, it may be cost-effective to pursue active case detection (8). The evidence supporting this is currently based on modeling and is controversial given the high costs of screening and the fact that there are no studies that demonstrate either the cost or effectiveness of active case detection in a field setting in low-income countries. However, these models suggest that active screening may be cost-effective as an extension to DOTS for population groups where TB incidence is suspected to be high. For example, the screening of contacts, prison populations, populations with high levels of HIV/AIDS and populations with suspected high rates of MDR-TB may be considered for screening.

As an intermediate approach to boost case detection, information, education and communication (IEC) is considered as an integral part of DOTS. In countries, which have low case detection rates together with high cure rates, significant investment in IEC may also be highly cost-effective. IEC can take many forms, from a doctor providing a patient with appropriate information on how TB is transmitted, to mass media campaigns. However, there are no studies either on the overall cost effectiveness of IEC for TB or the cost-effectiveness of
different methods. Unfortunately, it is also difficult to make estimates of cost-effectiveness based on IEC from other areas of health, as there is little evidence on the cost-effectiveness of IEC generally. This is because the effects of IEC have proven difficult to measure and attribute.

Finally, case detection rates can potentially be improved through collaboration with the private sector. However, so far there have been no studies in this area and little is known about the cost-effectiveness of public/private collaboration in TB control.

**Diagnosis by smear microscopy**
The WHO recommended method of diagnosis of pulmonary TB is smear microscopy. Sputum positive TB may also be diagnosed by a culture test. However, basic calculations suggest that smear microscopy is more cost-effective and less costly than culture (9). The effectiveness of microscopy is high and it requires less sophisticated and costly laboratory resources than culture testing. In addition, diagnosis is significantly faster and therefore reduces the time that the patient remains untreated and infectious. It is currently recommended that three consecutive sputum examinations are required for a smear test. There is some evidence that the third test may have a high incremental cost and therefore some argue that a policy of examining two samples should be considered in resource poor settings (10). This may be most applicable for populations with a high level of HIV infection, where laboratories may be over-burdened.

For TB suspects who cannot be diagnosed by smear microscopy, X-rays are the most commonly used method to identify suspect cases. However, although most cases of TB will show abnormalities on an X-ray\(^4\) (high sensitivity), abnormalities may also be due to a variety of other conditions (low positive predictive value). Sputum culture tests therefore also required to diagnose smear negative TB. There is no data on the comparative cost-effectiveness of X-ray and culture testing compared to culture testing alone. Finally, new diagnostic tools, such as the PCR test, are being developed which may be faster than normal culture testing and can be used for all TB cases. There are studies showing potential gains in cost-effectiveness from these technologies, however, it remains to be seen if they are feasible (11).

**Short Course Therapy**
Standardised short course regimens are an important element of DOTS. TB Programmes using short course therapies have consistently achieved higher cure rates than those relying on longer therapies. Short course therapies are more effective for two reasons: one, they are more efficacious; and two, compliance is higher. Importantly, short course therapies also reduce relapse rates and therefore multi-drug resistance. There is strong and consistent evidence that short course therapies are also more cost-effective. Several studies (7, 12,
13) find that although the short regimens are more expensive, the reduced length of treatment means that the overall cost to both the health service and the patient is lower.

**Compliance – Observation**

Evidence demonstrating that it is unnecessary to hospitalise TB patients for long periods to prevent transmission was established in the 1960’s, however many countries still treat TB on an inpatient basis. In addition as new short course treatments present few side effects, delivering treatment on an ambulatory basis through primary health services or the community is now feasible.\(^5\) However, ambulatory treatment is only effective if the level of compliance achieved is high. In the past, most ambulatory programmes relying on the self-administration of treatment failed to achieve high cure rates. The WHO therefore now recommends a policy of direct observation (DOT). In practice, direct observation means that patients should be observed taking their drugs for at least for the initial phase of treatment, (usually the first two months of treatment). This requires the close monitoring and follow-up of patients.

Countries applying DOT have achieved high cure rates with ambulatory treatment. However, there is some debate over whether these high rates are due to DOT or other elements of the DOTS strategy, such as the supervision of providers and improvements in programme management. This is important from an economic perspective, as the costs of DOT can be high, particularly in circumstances where health services are operating at full capacity and the incidence of TB is high. At the time of writing the debate on observation has not reached its conclusion. Some argue that multiple components might account for the success of DOTS and that focusing on direct observation as a key factor in the promotion of adherence is inappropriate. There is only one study examining the cost-effectiveness of DOT (14). It finds that self-administration is more cost-effective than supervision by health workers or family members. This paper has however, been strongly criticised, arguing that there is abundant evidence of the success of DOT from many countries, where high cure rates have been achieved. Compared to this, in the study none of the methods of observation examined had high cure rates, indicating that the DOT was not being correctly implemented (15).

Two additional points should be noted. Firstly, the definition of observation is variable. Observation in its widest sense means treatment that is not self-administered. In fact there are a variety of ways in which treatment can be considered as observed. Family and community members can play an important role in observation and this may be significantly more cost-effective than self-administration or health service observation (16, 17). Secondly, the studies to date have not examined the effects of observation on the incidence of MDR TB. A high treatment completion rate does not indicate whether the treatment was taken in a correct manner, which has consequences for MDR TB. This
however, is difficult to assess as MDR relapses may not reveal themselves until after treatment has been completed.

Another strategy to improve compliance is to provide patient incentives. Many successful TB programmes provide incentives or enablers to patients to complete treatment. These incentives come in several forms, such as: subsidised patient transportation, food packages, payments to the employers of patients, and monetary payments to the patient (18). The review referred to several unpublished studies examining whether these incentives provide added value and increase treatment completion; most are based in the US or Canada. Most of these studies (14 out of 17) show that incentives do improve programme performance. There are two studies that examine patient incentives in developing countries, one in Haiti and one in Bangladesh. Both find that groups receiving incentives are more likely complete treatment. However neither study looks at the incremental cost-effectiveness of incentives.

Incentives to Providers

Many TB Programmes face severe human resource constraints, not just in the absolute lack of staff, but also high rates of turnover and low motivation. In recent years there has therefore been a renewed interest in providing incentives to TB providers. Literature on the impact of incentive payments for staff in TB control is extremely limited, despite the widespread use of TB related incentives. The same review of all the studies identifies fifteen provider incentive schemes (18). Eight of the schemes use monetary incentives, with the remainder providing food, transportation or fuel. Incentives are given for different behaviours, cures, visits or referrals. There are two unpublished studies examining provider incentives in low-income countries. The first is from Bangladesh where incentive payments are made to community health workers and the second describes the national TB programme in China where incentives are provided to village doctors. Both schemes make payments at different points in diagnosis and treatment. Both studies show that the introduction of incentives was associated with increases in detection and completion. However, as with patient incentives no study was done of the incremental cost-effectiveness of the schemes.

The studies also raise several concerns about incentive schemes. Financial sustainability of schemes is a key concern, as external financing is responsible for financing in a large proportion of schemes. Secondly, there is also concern that schemes need sufficient monitoring to prevent misuse. In some instances the payment was formalised through a contract, however there is little known about the best form of contract and mechanism for contract monitoring.
Diagnosis and treatment of MDR-TB (DOTS-plus)

The main strategy to combat MDR-TB is DOTS. By ensuring that treatment is observed and consists of a combination of at least three different drugs, MDR-TB can be prevented. However, where outbreaks occur and MDR-TB is already prevalent, it may be necessary to include the treatment of MDR-TB as an extension to DOTS. Initial estimates of the cost of treating one patient in developed countries are in the tens of thousands of dollars. However, over the last few years there has been a considerable international effort to obtain concessional prices for MDR-TB drugs, and initial estimates of cost for low and middle countries are considerably lower than those in developed countries. The first study of the cost-effectiveness of the treatment of MDR-TB, from Peru (19) estimates the cost of treating one patient to be $2381, with the drugs cost estimated to be $824. It also estimates the cost per DALY to be somewhere between $200 and $300. This is well under $550 per DALY, the criteria established by the WDR 1993 for inclusion in essential packages in middle-income countries. Unlike the wealth of information on the different elements of DOTS, there are currently no strategies examining the cost-effectiveness of different elements of DOTS-plus. In particular little attention has been focused on the cost-effectiveness of case detection and the diagnosis of MDR-TB.

Collaborative TB HIV/AIDS Interventions

One of the most significant threats to TB control is the HIV/AIDS epidemic. Although DOTS remains the recommended strategy for TB control in high endemic HIV/AIDS environments, ways to adapt and integrate DOTS with HIV/AIDS strategies are currently being explored. Three interventions for those with living with HIV may also impact the TB epidemic: preventative therapy; HAART; and interventions which reduce the incidence of HIV.

Several studies show that the mass use of preventive therapy in developing countries is not likely to be as cost-effective as treating TB, as infection levels in the population are high and progression to TB is infrequent. In 1986, a study in Eastern Europe estimated that mass use of preventive therapy costs $7112 per case prevented, (over $550 per DALY in 2000 prices), using the most cost-effective regimen of 24 weeks (20). However, as HIV positive patients have a relatively high risk of developing active TB from infection, the possibility of providing preventive therapy routinely to HIV positive patients and family members of those with TB has been re-examined in the last few years. Although preventive therapy is efficacious, as with TB treatment, the effectiveness of the therapy depends primarily on whether a patient is prepared to comply with therapy, in this case for an illness that they do not yet have.

In one of the first studies modeling the potential benefits of preventive therapy, it was estimated that providing preventive therapy in South Africa would result
in a net saving of around $1 million over 8 years (21). This finding is supported by a study from Uganda (22). It finds that preventive therapy does not result in a reduction in future health service cost, if only the direct costs of HIV patients are examined. However, if social costs and the prevention of secondary cases are also included then preventive therapy will result in net savings. A study in Zambia (23) also supports this finding, and estimates a net cost if only direct costs are included, but significant net savings if lost patient income is taken into account. Excluding indirect and secondary benefits savings, the Ugandan study estimates the cost per DALY of preventive therapy at somewhere between $150 and $350. The reason for this relatively high figure is the assumption that TB preventative therapy will only have a small effect on the life expectancy of an HIV positive patient (8.37 years instead of 7.79 years) and the relatively low compliance rate.

Where TB is so strongly associated with HIV/AIDS, HIV/AIDS prevention can also be considered as intervention that controls TB. However, it is likely that reductions in HIV incidence will take several years before they impact TB incidence, although in the long term it still may prove to be cost-effective way of controlling TB. There is currently a debate over whether HAART should be seen as an effective TB control intervention. The application of HAART has been shown to reduce the incidence of TB in HIV/AIDS cases (2). However this effect may be temporary. In addition, the current body of economic evidence raises questions about the comparative cost-effectiveness and affordability of HAART (24). However, as the evidence base in this area very weak there needs to be a considerable amount further economic and operational research in this area before firm conclusions can be made.

In recent years the WHO has begun to work to develop a TB/HIV strategy, drawing on this evidence, for those countries significantly affected by HIV. Research is needed to establish cost-effectiveness of the package in a variety of settings.

Conclusion
This literature review summaries the evidence base on the cost-effectiveness of TB control strategies. Although the broad cost-effectiveness of DOTS has been established, it highlights several areas that still require further investigation, these include: the examination of the cost-effectiveness of re-structuring health services in middle income countries to provide DOTS; examination of new strategies for case detection, examination of new strategies/ tools to combat the growing threat of MDR-TB and assessing the cost-effectiveness of the integration of TB/HIV services. This thesis aims to support this broad effort, firstly by adding to the evidence base by estimating costs and cost-effectiveness of different TB control strategies, and secondly by examining ways in which to apply these results to estimate the total resource requirements of implementing TB control.
THE STUDY PROJECT GOALS AND OBJECTIVES

This thesis reports on a variety of studies exploring different elements of the TB control strategy. It focuses primarily on estimating the costs and cost-effectiveness of the implementation of DOTS, diagnostic strategies for MDR-TB, and expanding TB/HIV services, and the use of these results by decision makers.

Overall Goal

The ultimate goal of this thesis is to contribute towards improved case detection and control of TB, the development of local research capacity, and the use by TB policy makers and practitioners of economic analysis.

Objective

The main objective of this thesis is to assess the costs and cost-effectiveness of selected new TB control strategies in low and middle income countries and methodologies for applying these to decision making.

Specific Objectives

The specific objectives of this thesis are:
• To assess the cost-effectiveness of re-structuring TB control to DOTS in middle income countries: Egypt, Syria and Ukraine
• To assess the cost-effectiveness of adopting new technologies to tackle MDR-TB
• To assess the costs to the patient of integrated TB/HIV services
• To assess the methodologies used to estimate the costs of TB control (and HIV interventions) in low income countries

THE STRUCTURE OF THE THESIS

Chapter Two examines the cost-effectiveness of DOTS compared to other treatment strategies in Egypt and Syria. This chapter reports on the results of a study conducted half way through DOTS implementation in these two countries. Chapter Three examines the cost-effectiveness of DOTS compared to other treatment strategies in Ukraine. This chapter reports on the results of pilot projects and discusses the implications for national scale-up of DOTS. Chapter Four focuses on diagnostic technologies for MDR-TB. It reports on the results of an economic evaluation conducted as part of a clinical trial in Peru. Chapter Five presents the results of a study into the patient costs before and during the use of TB/HIV services. This study was part of a broader costing study into the costs of TB/HIV services in low income countries. Chapter
Six review the methods used to estimate the costs of TB and HIV interventions in sub-Saharan Africa. This review aims to inform national policy makers and planners on the use of costing studies in their medium term financial plans.

REFERENCES


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NOTES

1 This is now called WHO's (new) stop-TB strategy (Raviglione et al, Lancet 2006;367:952-5), however as this thesis was started before this change, this is referred to as DOTS throughout the thesis.

2 A partnership of international organisations committed to and active in TB control. This includes the WHO, World Bank and Unicef, NGO's, and MOHs.

3 The discussion section of this thesis updates this section in the light of the studies presented and those conducted by others on the same topics during the timeframe of this thesis.

4 Although this is less likely for HIV patients.

5 See above.

6 Also the length of time of preventive therapy, and whether to use a single drug.
The costs and cost-effectiveness of tuberculosis control