Achieving the millennium development goals for health

Cost effectiveness analysis of strategies for tuberculosis control in developing countries

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This article is part of a series examining the cost effectiveness of strategies to achieve the millennium development goals for health

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Abstract

Objective To assess the costs and health effects of tuberculosis control interventions in Africa and South East Asia in the context of the millennium development goals.
Design Cost effectiveness analysis based on an epidemiological model.
Setting Analyses undertaken for two regions classified by WHO according to their epidemiological grouping—Afr-E, countries in sub-Saharan Africa with very high adult and high child mortality, and Sear-D, countries in South East Asia with high adult and high child mortality.
Data sources Published studies, costing databases, expert opinion.
Main outcome measures Costs per disability adjusted life year (DALY) averted in 2000 international dollars ($Int).
Results Treatment of new cases of smear-positive tuberculosis in DOTS programmes cost $Int6-8 per DALY averted in Afr-E and $Int7 per DALY averted in Sear-D at coverage levels of 50-95%. In Afr-E, adding treatment of smear-negative and extra-pulmonary cases at a coverage level of 95% cost $Int95 per DALY averted; the addition of DOTS-Plus treatment for multidrug resistant cases cost $Int123. In Sear-D, these costs were $Int52 and $Int226, respectively. The full combination of interventions could reduce prevalence and mortality by over 50% in Sear-D between 1990 and 2010, and by almost 50% between 2000 and 2010 in Afr-E.
Conclusions DOTS treatment of new smear-positive cases is the first priority in tuberculosis control, including in countries with high HIV prevalence. DOTS treatment of smear-negative and extra-pulmonary cases and DOTS-Plus treatment of multidrug resistant cases are also highly cost effective. To achieve the millennium development goal for tuberculosis control, substantial extra investment is needed to increase case finding and implement interventions on a wider scale.

Introduction

In developing countries, tuberculosis is second only to HIV/AIDS as the most common cause of adult death and is a top public health problem almost everywhere. The United Nations millennium development goals include targets for tuberculosis control, now adopted and extended by the international Stop TB Partnership. The targets include reversing tuberculosis incidence by 2015, halving tuberculosis prevalence and mortality by 2015 (compared with 1990), and diagnosing 70% of new smear-positive cases and curing 85% of these cases by 2015 (see bmj.com).[1]

For many countries, the targets will not be achieved at current rates of progress.[2] This means that an important question is whether the correct mix of interventions is currently being used, and what strategies should be scaled up if current international efforts to raise extra funds for health care are successful. Cost and cost effectiveness analyses can help with these decisions.

The main interventions recommended to control tuberculosis are short course treatment with first line drugs for drug-susceptible tuberculosis (smear-positive pulmonary, smear-negative pulmonary, and extra-pulmonary) within the framework of the DOTS strategy, and treatment of cases with multidrug resistant tuberculosis with longer and more complex drug regimens that include second line as well as first line drugs within the framework of the DOTS-Plus strategy (see bmj.com for details).

To date, most economic studies of tuberculosis interventions in developing countries have evaluated short course treatment for drug susceptible, smear-positive pulmonary tuberculosis,[3–5] since this is the most infectious form of the disease. Most studies are from Africa,[6] although Asia has the highest burden of tuberculosis. Two studies have also reported the cost effectiveness of treating smear-negative cases.[7 8] One study, from Peru, reports treatment for multidrug resistant tuberculosis with first line and second line drugs.[9]

Most studies did not assess the impact of interventions on transmission, and most used indicators of effectiveness that are specific to tuberculosis control, preventing the cost effectiveness being compared with

P+ *Further details of the methods used appear on bmj.com*

ELPS *This is the abridged version of an article that was posted on bmj.com on 10 November 2005: http://bmj.com/cgi/doi/10.1136/bmj.38645.660093.68*

that of interventions for other diseases. Moreover, interventions have generally been considered individually, not in combination.

In this paper we address the question of what are the costs and effects of treatment of new smear-positive cases and of new smear-negative and extra-pulmonary cases in DOTS programmes, and of DOTS-Plus treatment for multidrug resistant cases that have not responded to first line treatments, both singly and in combination. Our analysis includes assessment of the impact of interventions on transmission, a generic measure of effectiveness, and covers Asia as well as Africa.

Methods

General approach

We evaluated interventions for two particular regions classified by the World Health Organization: Afr-E, countries in sub-Saharan Africa with very high adult and high child mortality, and Sear-D, countries in South East Asia with high adult and high child mortality.[10] (See bmj.com for existing levels of tuberculosis control globally and these two regions.)

Interventions run for the 10 years 2000-9. We included all benefits accruing during the period 2000-100. We evaluated the three standard levels of geographical coverage—50%, 80%, and 95%—which in this case mean the percentage of eligible cases living in areas where treatment is available. We assessed costs from a societal perspective, and used a population model to translate disease-specific results into a generic measure of health effects. See Evans et al for details of the standardised analytical approach.[10]

Interventions

We restricted our analysis to four interventions:

Minimal DOTS—Treatment in DOTS programmes for new smear-positive cases only. We assume the percentage of cases diagnosed and treated in areas covered by DOTS increases linearly from year 2000 levels to the WHO target of 70% in 2009 and the cure rate is at the WHO target level of 85% from 2000 to 2009. In areas not covered by DOTS, we assume no cases are treated. In all areas, no cases are treated from 2010 onwards.

Full DOTS—As for minimal DOTS plus treatment of smear-negative and extra-pulmonary cases in DOTS programmes. We assume the percentage of cases diagnosed and cured is the same as for smear-positive cases.

Minimal DOTS plus resistant cases—As for minimal DOTS plus treatment of multidrug resistant cases in DOTS-Plus programmes with an 18 month regimen that includes first and second line drugs. We assume patients are tested for multidrug resistance after failing treatment with the short course of first line drugs. We assume the cure rate to vary from 48% (baseline analysis) to 70% (sensitivity analysis).[9]

Full combination—As for full DOTS plus DOTS-Plus treatment for multidrug resistant tuberculosis as defined above.

The maximum scale at which we considered each intervention is much greater than the level of tuberculosis control efforts in 2003.

Estimating health effects

We estimated health effects in three steps. Firstly, we calibrated a published tuberculosis-HIV model[11 12] to produce tuberculosis incidence, prevalence, and mortality for each region that matched those observed between 1950 and 2000 (see bmj.com for details).

Secondly, we used the calibrated tuberculosis-HIV model to project incidence, prevalence, and mortality for the period 2000 to 2100 for the base case of no interventions, and then for each of the intervention scenarios.

Thirdly, we used the population model PopMod[13] to combine the projected incidence, prevalence, and mortality data with the standard health state valuations[14] to estimate the population impact of the different interventions in terms of healthy years lived.[10] We ran the model for the length of time necessary for all people affected by the interventions to have died. The

Table 1 Annual numbers of patients treated, total costs in international dollars ($Int), total effects, and average and incremental cost effectiveness for various tuberculosis control interventions in the Afr-E region

Intervention*	Coverage level	No of patients treated (millions)			Total costs ($Int millions)	Yearly DALYs averted (millions)	Cost per DALY averted ($Int)	
		New smear-positive cases	New smear-negative and extra-pulmonary cases	Multidrug resistant cases			Average	Incremental†
Minimal DOTS	50%	0.33	NA	NA	146.3	23.6	6.2	6.2
	80%	0.52	NA	NA	262.6	37.7	7.0	8.2
	95%	0.62	NA	NA	366.3	44.8	8.2	14.7
Full DOTS	50%	0.32	0.27	NA	242.4	24.9	9.7	NA
	80%	0.52	0.43	NA	439.6	39.9	11.0	NA
	95%	0.62	0.51	NA	612.2	47.4	12.9	94.5
Minimal DOTS plus resistant cases	50%	0.32	NA	0.01	184.1	24.1	7.6	NA
	80%	0.51	NA	0.02	343.4	38.6	8.9	NA
	95%	0.61	NA	0.03	495.9	45.9	10.8	NA
Full combination	50%	0.32	0.27	0.01	279.1	25.5	11.0	NA
	80%	0.51	0.43	0.02	518.6	40.8	12.7	NA
	95%	0.61	0.51	0.03	739.4	48.4	15.3	123.2

Values are averages over the 10 year evaluation period. Costs are given in international dollars (a hypothetical unit of currency that has the same purchasing power that the US$ has in the United States at a given point in time) and can be converted into US$ for a reference country in a region. For example, cost estimates in Afr-E in $Int should be divided by 4.5 to obtain US$ cost estimates for Kenya. Details of this approach are discussed elsewhere.[18]

NA=Not applicable.

*See methods section for details of interventions.

†Incremental costs per DALY averted measure the increase in cost divided by the increase in effects when a new intervention is added to an existing intervention. Values are not shown for interventions that are dominated (more costly but less effective than others).

Table 2 Annual numbers of patients treated, total costs in international dollars ($Int), total effects, and average and incremental cost effectiveness for various tuberculosis control interventions in the Sear-D region

Intervention*	Coverage level	No of patients treated (millions)			Yearly costs ($Int millions)	Yearly DALYs averted (millions)	Cost per DALY averted ($Int)	
		New smear-positive cases	New smear-negative and extra-pulmonary cases	Multidrug resistant cases			Average	Incremental†
Minimal DOTS	50%	0.73	NA	NA	293.1	40.3	7.3	NA
	80%	1.16	NA	NA	442.6	64.5	6.9	6.9
	95%	1.38	NA	NA	536.4	76.6	7.0	7.8
Full DOTS	50%	0.72	0.25	NA	473.7	43.9	10.8	NA
	80%	1.15	0.40	NA	731.7	70.2	10.4	NA
	95%	1.37	0.47	NA	883.4	83.4	10.6	51.6
Minimal DOTS plus resistant cases	50%	0.72	NA	0.10	500.4	41.3	12.1	NA
	80%	1.15	NA	0.16	773.4	66.0	11.7	NA
	95%	1.36	NA	0.18	932.6	78.4	11.9	NA
Full combination	50%	0.71	0.25	0.10	677.4	44.8	15.1	NA
	80%	1.14	0.39	0.15	1056.7	71.6	14.7	NA
	95%	1.35	0.47	0.18	1272.7	85.1	15.0	226.4

Values are averages over the 10 year evaluation period. Costs are given in international dollars (a hypothetical unit of currency that has the same purchasing power that the US$ has in the United States at a given point in time) and can be converted into US$ for a reference country in a region. For example, cost estimates in Sear-D in $Int should be divided by 5.2 to obtain US$ cost estimates for India. Details of this approach are discussed elsewhere.[18]
NA=Not applicable.
*See methods section for details of interventions.
†Incremental costs per DALY averted measure the increase in cost divided by the increase in effects when a new intervention is added to an existing intervention. Values are not shown for interventions that are dominated (more costly but less effective than others).

difference between the healthy years lived in each intervention scenario and the no-intervention scenario is the health gain of the intervention, or the number of disability adjusted life years (DALYs) averted.

Estimating costs

We based our estimates of the resources required—diagnostic tests, drug use, health centre visits for supervision and monitoring, and hospitalisation—for each intervention on WHO treatment protocols and expert opinion. We combined unit costs with patterns of resource use to estimate the cost per patient treated, and calculated total patient costs as the cost per patient treated multiplied by the number of patients treated. We estimated the costs of running the programmes using a standardised approach.[10] All costs are reported in international dollars ($Int) for the year 2000, and the conversion from $Int to US$ is explained elsewhere.[10]

Results

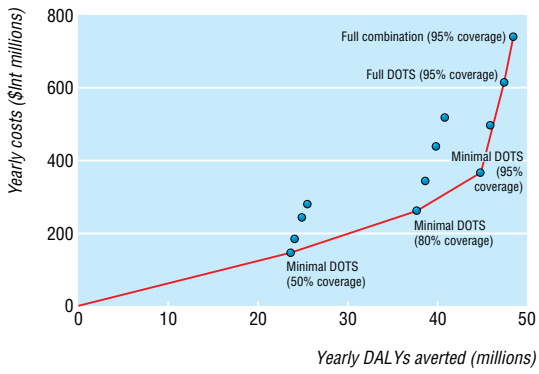
The tuberculosis model replicated the strong increase in the incidence of infectious disease in Afr-E from around 1990, with an annual growth rate of about 10% between 1990 and 2000. In Sear-D, the tuberculosis model estimates an annual decline in incidence of 1% in the same period.

Intervention effects

Tables 1 and 2 show the health effects, costs, and cost effectiveness of the different interventions in Afr-E and Sear-D. When only smear-positive cases are treated in DOTS programmes and the geographical coverage level is 95%, an average of 0.62 million people are treated in Afr-E and 1.38 million in Sear-D each year. The annual cost averages $Int366m in Afr-E and $Int536m in Sear-D. The total number of DALYs averted per year averages 44.8 million in Afr-E and 76.6 million in Sear-D. Adding treatment of smear-negative and extra-pulmonary cases or of multidrug resistance cases increases costs considerably but increases the DALYs averted only slightly. Increasing the coverage level from 50% to 95% roughly doubles both costs and effects for each of the four interventions considered.

In both regions, treating only smear-positive cases is the most cost effective intervention, with an average cost per DALY averted of ≤ $Int8 at all coverage levels. The next most cost effective intervention in both regions is treatment for both smear-positive and smear-negative and extra-pulmonary cases at a coverage level of 95%, at a cost per DALY averted of $Int95 in Afr-E and $Int52 in Sear-D. This is followed by implementing the full combination of interventions, including treatment for multidrug resistant tuberculosis, at a cost per DALY averted of $Int123 in Afr-E and $Int226 in Sear-D.

Treating only smear-positive cases at a coverage level of 50% would be introduced first for Afr-E (figure). With more resources, coverage would be expanded to 80% and then to 95%. With yet more resources, treatment of smear-negative and extra-pulmonary cases would be introduced, followed by the addition of treatment for multidrug resistant cases. The expansion path is similar in Sear-D.



Expansion path for tuberculosis interventions in Afr-E region according to average and incremental cost effectiveness. (See methods for description of interventions)

In Sear-D, our model suggests that implementing the full combination of interventions could reduce tuberculosis prevalence and mortality by 71% and 64% respectively between 1990 and 2010. In Afr-E prevalence and mortality increase substantially between 1990 and 2000, because of the HIV epidemic, but could fall by 50% and 40% respectively between 2000 and 2010.

Sensitivity and uncertainty analyses had little impact on our cost per DALY averted results for Afr-E or Sear-D (see bmj.com).

Discussion

Since the early 1990s, short course drug treatment for new smear-positive cases of tuberculosis has been promoted as one of the most cost effective healthcare interventions available, with a reported cost per DALY averted of US$1-3.[3] Our updated analysis, covering countries with some of the highest rates of tuberculosis infection in sub-Saharan Africa and South East Asia, supports this result, with the cost per DALY averted at around $Int8 (<US$2) in both regions. The addition of the other interventions that we considered—treatment of smear-negative and extra-pulmonary cases in DOTS programmes and treatment of multidrug resistant cases in DOTS-Plus programmes—is also highly cost effective compared with commonly used benchmarks.

Limitations of study

Some limitations are related to the general approach to cost effectiveness analysis, and are discussed elsewhere.[10] Limitations that are specific to this analysis for tuberculosis include the fact that we assumed that key model parameters such as tuberculosis transmission rates are the same across regions. Our assumption that multidrug resistant tuberculosis and drug susceptible tuberculosis are equally transmissible contrasts with the more conservative range of assumptions considered in an earlier study.[9] A further limitation is that we may have underestimated the costs of increasing the percentage of tuberculosis cases that are treated in DOTS programmes. Our study results may not be directly generalisable to other settings. However, studies for other regions using similar methods show similar results.[15]

Strengths of our study include the use of a tuberculosis model that has been widely applied,[12] consideration of combinations of interventions, inclusion of transmission in the analysis, use of a generic measure of effectiveness, and testing of important assumptions through sensitivity analyses.

Implications of results

Our results have three major policy implications. Firstly, they reinforce the principle that treatment of smear-positive cases in DOTS programmes must be the basis of any tuberculosis control strategy, as has become standard practice in almost all control programmes.

Secondly, they show that there is a strong economic case for treating smear-negative and extra-pulmonary cases in DOTS programmes and for treating multidrug resistant cases in DOTS-Plus programmes.

Finally, our study shows that substantial scaling up of all three interventions is needed in the next 10 years if the millennium development goal and related targets for tuberculosis control are to be reached. In particular, the case detection rate must be improved so that many more tuberculosis cases are diagnosed and successfully treated.

What is already known on this topic

Studies have shown DOTS treatment of new cases of smear-positive tuberculosis to be a cost effective intervention in Africa, but data for other regions of the world or for treating smear-negative and extra-pulmonary cases and multidrug resistant tuberculosis are scarce

Most studies have not considered the impact of interventions on transmission or interactions among interventions and have used measures of effectiveness that do not allow comparisons with other health interventions

What this study adds

This comprehensive and standardised analysis of different interventions in Africa and South East Asia accounts for both transmission and interactions among interventions

Treatment of smear-positive, smear-negative, and extra-pulmonary cases in DOTS programmes and treatment of multidrug resistant cases in DOTS-Plus programmes are cost effective in both regions

These results provide a strong case for substantial investment to improve case finding and to implement these interventions on a much wider scale

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Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study

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Abstract

Objective To examine whether the level of primary resistance to HIV drugs is increasing in the United Kingdom.
Design Multicentre observational study.
Setting All virology laboratories in the United Kingdom carrying out tests for HIV resistance as part of routine clinical care.
Participants 2357 people infected with HIV who were tested for resistance before receiving antiretroviral therapy.
Main outcome measure Prevalence of drug resistance on basis of the Stanford genotypic interpretation system.
Results Over the study period (February 1996 to May 2003), 335 (14.2%, 95% confidence interval 12.8% to 15.7%) samples had mutations that conferred resistance to one or more antiretroviral drugs (9.3% high level resistance, 5.9% medium level resistance). The prevalence of primary resistance has increased markedly over time, although patterns are specific to drug class; the largest increase was for non-nucleoside reverse transcriptase inhibitors. In 2002-3, the prevalence of resistance to any antiretroviral drug, to nucleoside or nucleotide reverse transcriptase inhibitors, to non-nucleoside reverse transcriptase inhibitors, or to protease inhibitors was 19.2% (15.7% to 23.2%), 12.4% (9.5% to 15.9%), 8.1% (5.8% to 11.1%), and 6.6% (4.4% to 9.3%), respectively. The risk of primary resistance was only weakly related to most demographic and clinical factors, including ethnicity and viral subtype.
Conclusions The United Kingdom has one of the highest reported rates of primary resistance to HIV drugs worldwide. Prevalence seems still to be increasing and is high in all demographic subgroups.

Introduction

Combination antiretroviral therapy has improved the prognosis of patients infected with HIV. Concerns are mounting that a secondary epidemic of drug resistant virus would render treatment less effective.[1–3] We describe a national surveillance scheme for HIV drug resistance on the basis of routine clinical samples. Of about 13 000 samples tested between 1996 and 2003, over 2300 were from patients who had never received antiretroviral therapy. We used these data to analyse the epidemiology of primary drug resistance in the United Kingdom, including temporal trends and associations with demographic and clinical factors.

Methods

The UK HIV drug resistance database is a repository of resistance tests carried out as part of routine care in the United Kingdom. The tests in our analysis were based on DNA sequencing of the *pol* gene. All sequences encompassed at least codons 4-99 of the protease gene and 34-234 of the reverse transcriptase gene. See bmj.com for data entered. Subtype was assigned using the STAR algorithm.[4]

We classified the patients' treatment status from several sources (see bmj.com). We defined a test as relating to recent infection if the patient was enrolled in the UK register of HIV seroconverters,[5] and the sample was taken within 18 months of a negative HIV antibody test result or other laboratory test result indicating acute infection.

We verified the information on therapy status for a sample of patients with one or two major mutations[6] and all patients with three or more major mutations. Information on antiretroviral therapy was incorrect in 26 (18%) of the 142 cases checked; we excluded these patients from the analysis.

The analysis includes all resistance tests on patients aged over 16 years who were naive to antiretroviral therapy. We used the Stanford HIVdb algorithm to assess the level of resistance to drugs[7]: a matrix of scores for each drug-mutation combination are summed across all mutations in the sample, and drug susceptibility is classified as "sensitive" (total score <15), "intermediate" (15-29), or "resistant" (≥ 30). We refer to the last two categories as medium level and high level resistance.

Statistical analysis

We derived confidence intervals for proportions using the "exact" method. Logistic regression analysis was used to examine the association between demographic and clinical factors and the prevalence of resistance,

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