Cost-Effectiveness of Various Tuberculosis Control Strategies in Thailand

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A B S T R A C T

Objective: To evaluate the cost-effectiveness of different tuberculosis control strategies in Thailand. **Methods:** Different tuberculosis control strategies, which included health-worker, community-member, and family-member directly observed treatment (DOT) and a mobile phone "contact-reminder" system, were compared with self-administered treatment (SAT). Cost-effectiveness analysis was undertaken by using a decision tree model. Costs (2005 international dollars [I\$]) were calculated on the basis of treatment periods and treatment outcomes. Health outcomes were estimated over the lifetime of smear-positive pulmonary tuberculosis patients in disability-adjusted life years (DALYs) averted on the basis of Thai evidence on the efficacy of the selected strategies. **Results:** Cost-effectiveness results indicate no preference for any strategy. The uncertainty ranges surrounding the health benefits were wide, including a sizeable probability that SAT could lead to more health gain than DOT strategies. The health gain for family-member DOT was 9400 DALYs (95% uncertainty interval −7200 to 25,000), for community-member DOT was 13,000 DALYs (95% uncer-

tainty interval −21,000 to 37,000), and for health-worker DOT was 7900 DALYs (95% uncertainty interval −50,000 to 43,000). There were cost savings (from less multi-drug resistant tuberculosis treatment) associated with family-member DOT (−I\$9 million [95% uncertainty interval −I\$12 million to −I\$5 million]) because the trial treatment failure rate was significantly lower than that for SAT. The mobile phone reminder system was not cost-effective, because the mortality rate associated with it was much higher than that associated with other treatment strategies. **Conclusions:** Because of the large uncertainty intervals around health gain for DOT strategies, it remains inconclusive whether DOT strategies are more cost-effective than SAT. It is evident, however, that family-member DOT is a cost-saving intervention.
Keywords: cost-effectiveness, DOT, mobile phone reminder, self-administered treatment, Thailand, tuberculosis.

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Introduction

Tuberculosis (TB) remains one of the global leading public health problems. In 2007, Thailand ranked 18th out of the 22 high-burden countries globally. Thailand has met one of the global targets that have been set by the World Health Assembly and the Stop TB Partnership as well as are within the framework of the Millennium Development Goals, for 70% detection of new smear-positive cases but has not yet achieved successful treatment of 85% [1].

Effective cure of TB requires a patient taking medication without interruption following a strict schedule for at least 6 months, which is difficult for most patients to maintain. Directly observed treatment (DOT), whereby a trained person observes patients taking their medications, is widely used to improve adherence to treatment. It is worth noting that DOT and DOTS (directly observed treatment, short course) are different terms. DOT is one of the five key components of DOTS, which is recommended by the World Health Organization (WHO) [2]. The five key components are 1) government commitment, 2) case detection by sputum smear microscopy, 3) standardized treat-

ment regimen with DOT, 4) a regular drug supply, and 5) a standardized recoding and reporting system. There are three DOT options commonly used: health worker, community member, and family member [3,4].

There have been a few cost-effectiveness studies comparing DOT to self-administered treatment (SAT), but none has been conducted in Thailand [5,6]. A Cochrane review found no evidence that DOT shows better cure rates than does SAT [7]; however, a Thai trial [8] that was included in the review showed that DOT provides modest additional benefits.

Recently, mobile phones have gained attention in health care. As mobile technologies improve health systems and the delivery of health care [9], several researchers have shown evidence that mobile phones have the potential to improve health outcomes in the developing world [10]. There have been a few studies of the use of mobile phone in a TB control program [9,11,12]. To our knowledge, no other studies have evaluated the cost-effectiveness of the mobile phone intervention compared with that of SAT. In this article, we evaluated the cost-effectiveness of five different strategies, including different DOT options, mobile phone intervention, and SAT.

Fig. 1 – Decision tree of different TB control strategies. CM, community member; D, died; DOT, directly observed treatment; FM, family member; HIV–, HIV negative; HW, health worker; MDR-TB, multi-drug resistant tuberculosis; PTB, pulmonary tuberculosis; S, successful treatment; SAT, self-administered treatment; SS+, sputum smear-positive; T, transferred out.

Methods

Interventions and comparator

We reviewed the TB control strategy literature to identify interventions that would be suitable to implement in Thailand and had evidence of efficacy to support the analyses. The three DOT options are recommended methods of supervision by the WHO, depending on

the distance between a patient's place and a health facility [4], while mobile phone intervention has become an interesting alternative as it has become ubiquitous. Five interventions were included in the cost-effectiveness analysis: health-worker DOT, community-member DOT, family-member DOT, mobile phone "contact-reminder" system, and SAT. We used SAT as the comparator for each DOT strategy and the mobile phone intervention. A description of each intervention is as follows:

Table 1 – Effects of interventions.				
Intervention	Success rate (95% CI)	Failure rate (95% CI)	Transfer out rate (95% CI)	Death rate (95% CI)
DOT by an HW	0.87 (0.70–0.97)	0.04 (0.00–0.15)	0.00 (0.00–0.00)	0.09 (0.01–0.24)
DOT by a CM	0.79 (0.64–0.91)	0.15 (0.05–0.28)	0.03 (0.00–0.11)	0.03 (0.00–0.10)
DOT by an FM	0.84 (0.80–0.88)	0.08 (0.05–0.11)	0.02 (0.01–0.04)	0.06 (0.04–0.09)
Mobile phone	0.82 (0.72–0.90)	0.01 (0.00–0.05)	0.00 (0.00–0.00)	0.17 (0.09–0.26)
SAT	0.76 (0.72–0.80)	0.14 (0.11–0.18)	0.05 (0.03–0.07)	0.05 (0.03–0.07)

CI, confidence interval; CM, community member; DOT, directly observed treatment; FM, family member; HW, health worker; SAT, self-administered treatment.

DOT: Patients' drug intake is supervised daily for 6 months by a health worker at a health-care facility (health-worker DOT), a village health volunteer (community-member DOT), or a family member (family-member DOT) at the patients' home.

Mobile phone "contact-reminder": For 6 months, patients are reminded via a mobile phone to take their daily medication by village health volunteers who have previously completed their own TB treatment.

SAT: Patients take their daily medication without supervision for 6 months.

For all interventions, patients are followed up twice per month in the first 2 months and monthly thereafter either at home or in a health-care facility by health workers.

Tuberculosis model

The cost-effectiveness of the selected TB control strategies was evaluated in a decision tree model. The model was constructed in Microsoft Excel with the add-in tool Ersatz (www.epigear.com) for uncertainty analysis.

The model has three stages of treatment: initial treatment, re-treatment, and multi-drug resistant TB (MDR-TB) treatment (Fig. 1). A patient who fails the initial treatment is treated again in stage two called "re-treatment." A retreated patient who fails re-treatment is treated again in stage three called "MDR-TB treatment." The treatment period varies according to the stage of treatment [13–15]. The initial treatment lasts 6 months, the retreatment lasts 8 months, and the MDR-TB treatment lasts 18 months. We used standard treatment outcome definitions from the WHO [1], grouped into four categories: successful treatment (cured or treatment completed), failed (treatment failure or defaulted), transferred out, or died. For each intervention, a patient can follow one of nine possible pathways: success1, success2, success3, transfer1, transfer2, transfer3, die1, die2, or die3 (Fig. 1).

Probabilities of treatment outcomes from the initial treatment are different by interventions and comparator. Treatment outcomes from DOT interventions and SAT were derived from a Thai randomized controlled trial [8]. Treatment outcomes from the mobile phone intervention were derived from a mobile phone monitoring care study [12]. Table 1 shows treatment outcomes of each intervention. We assumed that each intervention had the same set of probabilities of treatment outcomes for retreatment and MDR-TB treatment. These probabilities were derived from the National TB Program [16] and an MDR-TB study conducted in Thailand [17], respectively.

We focused our study on treated HIV-negative TB patients who were sputum smear-positive and were aged 15 years or more (18,313 males and 7502 females), because these are the target populations in the efficacy studies. The number of treated patients was derived from case notification reporting from the National TB Program [18,19] and corrected for 13% underreporting of non-Thai patients and patients treated in the private sector [20]. Multiplying the adjusted case notifications with one minus HIV prevalence (24%) among TB patients [20] gives the number of HIV-negative TB cases.

To estimate MDR-TB incidence, we multiplied the failure rate from the initial treatment and the failure rate from the retreatment with the number of patients treated.

Estimating health outcomes

The health outcomes were estimated over their lifetime in disability-adjusted life years (DALYs), the measure introduced by the WHO [21], rather than in quality-adjusted life years. This was done because the calculation of DALYs has more advantages (e.g., when comparing among interventions for many diseases) from using a standard set of weights across all diseases while the calculation of quality-adjusted life years does not have these advantages (it is

Table 2 – Uncertainty distributions around parameters for estimating health outcomes.				
Parameter	Value	Distribution	Sources	Intervention
Pulmonary TB disability weight	0.29, 95% CI 0.181–0.406	Beta	[27]	All interventions
Numbers of outcomes for initial treatment	N = 24, n1 = 21, n2 = 1, n3 = 2, n4 = 0	Dirichlet	[8]	Health-worker DOT
	N = 34, n1 = 27, n2 = 5, n3 = 1, n4 = 1	Dirichlet	[8]	Community-member DOT
	N = 352, n1 = 297, n2 = 27, n3 = 21, n4 = 7	Dirichlet	[8]	Family-member DOT
	N = 71, n1 = 58, n2 = 1, n3 = 12, n4 = 0	Dirichlet	[12]	Mobile phone reminder
	N = 422, n1 = 320, n2 = 61, n3 = 21, n4 = 20	Dirichlet	[8]	SAT
Numbers of outcomes in untreated group	N = 126, n1 = 35, n2 = 53, n3 = 38	Dirichlet	[32]	All interventions
Numbers of outcomes for retreatment	N = 967, n1 = 612, n2 = 216, n3 = 92, n4 = 47	Dirichlet	[16]	All interventions
Numbers of outcomes for MDR-TB treatment	N = 13, n1 = 5, n2 = 0, n3 = 2, n4 = 6	Dirichlet	[17]	All interventions

CI, confidence interval; DOT, directly observed treatment; MDR-TB, multi-drug resistant tuberculosis; N, total number; n1, number successfully treated; n2, number of failed treatments; n3, number of deaths; n4, number of cases transferred out; RCT, randomized controlled trial; SAT, self-administered treatment; TB, tuberculosis.

Table 3 – Costs of each intervention with 95% uncertainty intervals for 25,815 treated patients.			
Intervention	Government costs (I$ million)	Patient costs (I$ million)	Total costs (I$ million)
DOT by an HW	23 (19–29)	19 (16–23)	42 (36–50)
DOT by a CM	23 (17–31)	3 (2–5)	26 (19–35)
DOT by an FM	17 (15–19)	3 (2–3)	20 (18–22)
Mobile phone	19 (17–21)	1 (1–2)	20 (18–23)
SAT	26 (23–28)	3 (3–4)	29 (26–32)

CM, community member; DOT, directly observed treatment; FM, family member; HW, health worker; I$, international dollars; SAT, self-administered treatment.

based on overall health status but not for specific disease). This study was one part of a project aimed at comparing various interventions from different diseases. Therefore, DALYs was our preferred choice.

There were two steps to calculate the DALYs for each intervention. First, we estimated the health-adjusted life expectancy of each pathway by using a life-table approach. The *health-adjusted life expectancy* is an estimate of the average years of equivalent "full health" life that a person can expect to live at various ages taking into account years lived in less than full health due to disease and/or injury (disability) [22]. Age- and sex-specific TB and background mortality rates used to calculate health-adjusted life expectancy were derived from a Thai cause of death study [23]. That study undertook cause of death ascertainment by using verbal autopsy interviews and hospital records to improve cause of death data in Thailand because the routine vital registration data has almost 40% of records with an ill-defined cause [24–26]. The total number of deaths in Thailand was increased from those recorded in the vital registration system by correcting for underreporting by using the 2005-2006 Survey of Population Change [23]. The corrected cause profiles from the verbal autopsy interviews and medical record reviews were applied to this estimate of total deaths by using proportionate mortality by age and sex. The disability weight for TB, which estimates the amount of time lost to ill health per year, was obtained from a Dutch disability weights study [27], and the disability weight for all other causes was derived from the Thai Burden of Disease and Injuries study [28] as the per capita rate of prevalent years lived with disability from all causes apart from TB.

Second, we calculated an expected health-adjusted life expectancy of each intervention as the sum of the health-adjusted life expectancy of all pathways weighted by the probability of each pathway. The difference between the expected health-adjusted life expectancy of each intervention and the comparator scenario multiplied with the number of patients treated was the health gain of the intervention in DALYs averted. Health outcomes were referenced to 2005 and discounted at 3% per annum.

Table 4 – Estimated number of MDR-TB incidence for all interventions.	
Intervention	MDR-TB incidence (95% CI)
DOT by an HW	244 (6–915)
DOT by a CM	852 (300–1650)
DOT by an FM	439 (284–625)
Mobile phone	82 (2–311)
SAT	833 (638–1071)

CI, confidence interval; CM, community member; DOT, directly observed treatment; FM, family member; HW, health worker; MDR-TB, multi-drug resistant tuberculosis; SAT, self-administered treatment.

Estimating costs

Costs for treating those patients were estimated according to treatment period and pathway. We divided costs into two categories: intervention costs and medical costs. Each cost category was calculated by using the health-care perspective, incorporating costs borne by both the government and patients. All costs were measured by using a standardized ingredients approach, requiring information on the quantities of all resources used and their unit costs. Total costs were quantities of inputs multiplied with their unit costs.

Intervention costs were any costs associated with the intervention. Intervention costs incurred by the government were costs from health staff supervision and monitoring time, travel costs to monitor patients at home, and mobile phone monitoring care. Intervention costs incurred by patients were travel and time costs to be supervised or followed up.

Medical costs were the general costs for treating TB patients, which did not differ by intervention. For instance, medical costs incurred by the government included laboratory costs (direct smear examination, sputum culture, drug susceptibility test), pharmaceutical costs, and the costs of radiology and health facility. Medical costs incurred by patients and families comprised travel and time costs to or at health facility and out-of-pocket expenses (costs for food and drink).

All costs were reported in international dollars (I$), a hypothetical currency representing the purchasing power of local currency in a corresponding country, which is equivalent to the purchasing power of US dollar in the United States [29]. One I$ was equal to 12.12 Thai baht for 2005 [30]. The same idea of calculating the weighted average health-adjusted life expectancy was applied to calculate a weighted average cost. Future costs were discounted to 2005 values by using a 3% discount rate. Details of all costs are described in Supplemental Material found at doi:10.1016/j.jval.2011.11.006.

Cost-effectiveness analysis

An incremental cost-effectiveness ratio (ICER) was evaluated for each intervention. The ICER was calculated by dividing the incremental cost (intervention cost minus comparator cost) by the DALYs averted. We adopted cost-effectiveness thresholds from the CHOosing Interventions that are Cost Effective project [31]. These thresholds are 1) highly cost-effective when the ICER is less than one time the gross domestic product per capita per DALY and 2) cost-effective when the ICER is less than three times the gross domestic product per capita per DALY. Ninety-five percent uncertainty intervals were determined for all outcome measures by using Monte Carlo simulation with 2000 iterations in Ersatz (www.epigear.com). Uncertainty distributions surrounding parameters for estimating health outcomes are provided in Table 2. We used beta distribution for disability weight (value between 0 and 1). The beta distribution requires two parameters: alpha1 and alpha2. These parameters can be derived from sample mean and variance by using the method of moments. A Dirichlet distribution is used for numbers of treatment outcomes that have more than

Table 5 – Cost-effectiveness of TB control interventions with 95% uncertainty intervals when compared with SAT.			
Intervention	Incremental costs (I$ million)	DALYs averted	Median ICER (I$/DALY)
DOT by an HW	13 (7–22)	7,900 (−50,000 to 43,000)	1,100 (270 to dominated)
DOT by a CM	−3 (−11 to 7)	13,000 (−21,000 to 37,000)	Dominant (dominant to dominated)
DOT by an FM	−9 (−12 to −5)	9,400 (−7,200 to 25,000)	Dominant (dominant to 1,300)
Mobile phone	−9 (−12 to −5)	−26,000 (−68,000 to 11,000)	350 (dominant to 120)

All results are shown rounded to two significant digits.
CM, community member; DALYs, disability-adjusted life years; DOT, directly observed treatment; FM, family member; HW, health worker; ICER, incremental cost-effectiveness ratio; I$, international dollars; SAT, self-administered treatment.

two outcomes. This distribution is the multivariate generalization of the beta distribution for multinomial data, which can be used to represent the proportions of those treatment outcomes.

All input parameters for estimating costs were not obtained from a sample observation but from a population observation or a report or an expert's opinion, and therefore there was no sampling uncertainty. We used a Pert distribution to model uncertainty around all cost parameters. The Pert distribution is a rescaled and reparametrized beta distribution [33] that requires three parameters: minimum, mode, and maximum values. The maximum and minimum values for the government cost and the patient cost were assumed to be ±10% and ±25% of the mode values, respectively.

Results

Table 3 shows government, patient, and total costs of each intervention. SAT was the most expensive intervention to the government, more expensive than health-worker DOT. This was due to the higher failure rate of SAT compared with that of health-worker DOT (Table 1). The high failure rate of SAT resulted in a high estimate of MDR-TB incidence (Table 4). And consequently, there were greater costs for MDR-TB treatment. Health-worker DOT was the most expensive intervention from the patient perspective. It involved substantial travel and time costs to be supervised at the health center.

Cost-effectiveness results did not clearly indicate a preference for any of the interventions analyzed. The median ICER for health-worker DOT, community-member DOT, and family-member DOT was I$1100 per DALY, dominant (less costly, more DALYs averted), and dominant, respectively. Although the median ICERs for DOT interventions were favorable with the median ICER below the threshold of one time gross domestic product per capita per DALY or I$9000 per DALY, the uncertainty ranges around the health gain in DALYs were wide and crossed zero (Table 5 and Fig. 2), indicating that no distinction could be made in cost-effectiveness between any of the DOT options and SAT. There were cost savings (from less retreatment or MDR-TB treatment) associated with family-member DOT at –I$9 million (95% uncertainty interval −I$12 million to –I$5 million) (Fig. 2) because the trial treatment failure rate was significantly lower than that for SAT.

Although the mobile phone intervention was cheaper than SAT (Table 5), this intervention led to less health gain. As can be seen in Figure 2, mobile phone reminder predominantly fell in the southwest quadrant of the cost-effectiveness plane, indicating a cost-saving for less health gain.

Discussion

Effects of the interventions in this study had wide overlapping confidence intervals because results were derived from small studies. Therefore, we could not state which intervention was the most cost-effective. The median ICERs of our DOT interventions were as favorable as the results from a study in Brazil [6], with a median ICER of $86 per DALY averted (less than the $2710-per-DALY threshold) for DOT (unknown observer type) compared with SAT. However, the Brazilian study showed narrower uncertainty ranges around the health benefits than did the current study. This may be due to its use of efficacy from a larger cohort. Although the exact size of the cohort of the Brazilian study was not stated, it can be presumed that it was much larger than the cohort of our study because the Brazilian study was based on programmatic outcomes from all cases recorded by the Health Department in Rio de Janeiro. We adopted intervention effects from a small (836 participants) randomized controlled trial, which had wide 95% confidence intervals and overlap between different interventions.

A study from Pakistan [5] found that DOT interventions were not favorable because SAT was the lowest cost intervention ($164 per case cured). This may be because the time horizon for the study in Pakistan was 8 months, which included only the cost for initial treatment but not the treatment costs associated with treatment failure and drug resistance. This may have contributed to a lower cost for SAT despite it having the highest default rate [34]. The results from the Pakistan study could not be compared with our results as there was difference in outcome measurement (DALYs averted vs. cases cured). We took all treatment outcomes (cured, treatment completed, treatment failure, died, defaulted, and transferred out) of each intervention into account when calculating the health outcome through a patient's lifetime, whereas the study from Pakistan focused only on cases cured.

Although the mobile phone intervention was cheaper than SAT, the health gain was much less (Table 5). This was due to the mortality rate in the small trial (70 patients) of this intervention being much higher than for each of the other treatment strategies.
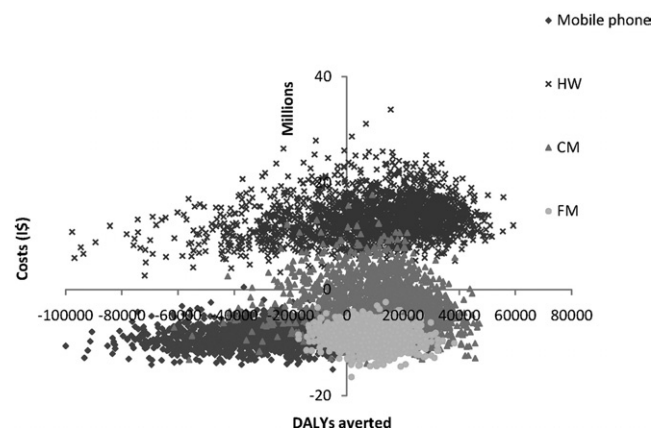
Fig. 2 – Cost-effectiveness of the TB control interventions when compared with SAT. CM, directly observed treatment by a community member; DALY, disability-adjusted life years; FM, directly observed treatment by a family member; HW, directly observed treatment by a health worker; I$, international dollar; SAT, self-administered treatment.

Authors of the pilot study, however, stated that the high mortality rate was likely to have been due to the selection of an elderly population and comorbidities in this population rather than a result of the intervention. A bigger study with a control group and representative age distribution is needed to say more definitively what the merits of the mobile phone intervention are.

A key limitation of this study is the relatively weak evidence. Even though treatment outcomes of DOT interventions and SAT were obtained from a Thai randomized controlled trial, it was only a rather small trial. Moreover, an international meta-analysis as part of a Cochrane review [7] found no evidence that DOT interventions showed cure rates better than SAT. Nevertheless, some have argued that neither the Cochrane review nor the other research considers the main purpose of DOT, which is to prevent the development of resistance to rifampicin [35]. Our study considers all treatment outcomes rather than only cure rate to estimate cost and health outcomes from initial treatment through MDR-TB treatment.

In conclusion, because of the large uncertainty intervals around health gain for DOT strategies, it remains inconclusive whether DOT strategies are more cost-effective than SAT. It is evident, however, that family-member DOT costs are less than those for the alternative strategies.

Acknowledgments

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at doi: 10.1016/j.jval.2011.11.006 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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