

Original article

Costs and Cost-Effectiveness of Adolescent Compliance with Treatment for Latent Tuberculosis Infection: Results from a Randomized Trial

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Abstract

Purpose: Assess the costs and cost-effectiveness of an incentive-based tuberculosis (TB) program designed to promote adolescents' compliance with treatment for latent TB infection (LTBI).

Methods: Randomized controlled trial. Adolescents between the ages of 11 and 19 years who were referred to one of two participating clinics after being screened for TB and receiving a positive diagnosis indicating LTBI ($n = 794$) were assigned to one of four groups: usual care, peer counseling, contingency contracting, and combined peer counseling/contingency contracting. Primary outcome variables were completion of isoniazid preventive therapy (IPT), total treatment costs, and lifetime TB-related costs per quality-adjusted life year (QALY) in each of the four study groups (three treatment, one control). Cost effectiveness was evaluated using a five-stage Markov model and a Monte Carlo simulation with 10,000 trials.

Results: Average costs were \$199 for usual care (UC), \$277 for peer counseling (PC), \$326 for contingency contracting (CC), and \$341 for PC + CC combined. The differences among these groups were all significant at the $p = .001$ level. Only the PC + CC group improved the rate of IPT completion (83.8%) relative to usual care (75.9%) ($p = .051$), with an overall incremental CE ratio of \$209 per QALY relative to usual care.

Conclusion: Incentives combined with peer counseling are a cost-effective strategy for helping adolescents to complete care when combined with peer counseling. © 2007 Society for Adolescent Medicine. All rights reserved.

Keywords:

Adherence; Cost-effectiveness analysis; Health behaviors; Latent tuberculosis infection (LTBI)

Tuberculosis (TB) claims more lives worldwide than any other infectious disease. In 1997, TB was one of the leading causes of death from infectious diseases in the world, with 2.9 million reported deaths [1]. From 1985 through 1992, after decades of decline, TB reemerged in significant pro-

portions in the United States, increasing from 9.3 cases per 100,000 (22,201 total cases) to 10.5 cases per 100,000 (26,673 total cases) [2]. However, since 1993, there has been a continual decrease in the number of reported TB cases in the United States, especially in U.S.-born persons [3,4]. During 2004, the total number of reported TB cases in the United States was 14,511, or 4.9 cases per 100,000 [5]. Although the total number of cases is decreasing, the proportion of foreign-born TB cases in the United States is increasing [3,6,7]. While reflecting the changing trends in

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TB rates found in the rest of the United States, TB rates are high in California, particularly in Los Angeles County. New TB cases reported in Los Angeles County in 2004 (932) comprised almost 33% of California's TB incidence (2988 cases) and 6.4% of the total number of new cases in the United States. With the highest annual number of reported TB cases, California rates number one among states nationwide [5].

Adolescence is a time when activation of latent infection is more likely to occur [8]. The adolescent growth spurt is the time of greatest risk for the development of pulmonary tuberculosis as a result of infection. TB may be more aggressive within the adolescent patient due to hormonal changes and altered protein and calcium metabolism associated with adolescent growth [9,10].

With adolescents, measures need to be taken to ensure not only that the appropriate treatment is taken to eliminate the disease, but that the adolescents complete the full 6-month course of treatment, including daily medication, otherwise the latent TB infection (LTBI) is likely to reactivate. This is particularly relevant for those who are recent immigrants to the United States, who have a higher incidence of LTBI, including drug-resistant TB [11–13]. Compliance cannot always be achieved by simple prescription of the medication and the expectation that the adolescent will adhere to the full regimen, particularly because LTBI is asymptomatic [14,15]. Therefore, incentives such as tangible gifts, money, outings with friends, etc., may improve the course of care for LTBI treatment. However, are incentives a cost-effective strategy for increasing an adolescent's completion of care? The purpose of this study is to address this question by evaluating the costs and cost-effectiveness of an incentive-based LTBI treatment program.

Methods

Data and sample

This study was a preventive tuberculosis adherence study conducted in two public health clinics in Los Angeles County during 1995–1998. The two clinics were chosen because they had the greatest number of adolescents being treated for latent tuberculosis infection (LTBI). Adolescents between the ages of 11 and 19 years were recruited. The adolescents were referred to the clinic after being screened for tuberculosis at their school and receiving a positive diagnosis of LTBI, defined as a positive Mantoux skin test with an induration of 6 mm. The majority of the adolescents were screened as a requirement before attending school. The adolescents were recruited at their first clinic appointment. Active consent was obtained from the parents before the adolescent's recruitment, with a participation rate of 88%. Analysis of those who chose not to participate showed no difference relative to those who did participate with respect to demographic characteristics. Approval was obtained

from the UCLA Human Subjects Protection Committee for enrollment, data collection, and ongoing data analysis.

A total of 794 adolescents were recruited into the study and were randomly assigned to one of four groups: usual care (UC), peer counselor (PC), contingency contracting (CC) (i.e., an incentive agreed to between parent and adolescent), and combined peer counselor/contingency contracting (PC + CC). Randomization was based on six blocks, defined by three age groups and gender. Because each clinic treats a large volume of immigrant patients, language was not a barrier in recruiting study participants or in providing instructions for treatment. Questionnaires were available in English, Spanish, and Khmer (Cambodian). More information on the study design has been published elsewhere [16].

Variables

The primary dependent variables in this study are compliance (or adherence) with isoniazid preventive therapy (IPT) and total cost of LTBI treatment, compared across the four study groups. Compliance was defined as confirmation by a health care provider at each clinic verifying that the study participant had completed the 6-month course of treatment, as documented in the adolescent's medical record. To be compliant, the adolescent needed to attend the clinic at the end of the 6-month course treatment to report completion of the treatment. Because of the randomized design of the study, other covariates should be adequately controlled across groups. To assess whether compliance or total costs varied within each treatment group, we conducted a multivariate analysis of compliance and total cost, controlling for income, gender, student status, age, place of birth, self-rated overall health, difficulty in getting to clinic, length of time it took the adolescent to get to the clinic, living arrangement of the adolescent, and the length of time the adolescent waited to see a nurse.

Costs of TB treatment. We collected actual utilization data for individual services provided to study participants and then assigned costs to each individual service. Utilization data were obtained directly from an abstract of each adolescent's medical chart data. These included counts of: (1) clinic visits, (2) chest X-rays, (3) Mantoux tests, and (4) isoniazid prescriptions. The chart abstract also included counts of broken appointments, which we included in our cost estimates, because staff resources were expended in follow-up phone calls for patients with broken appointments. Direct costs of the intervention, including the cost of letters sent to the adolescents, the cost of hiring peer counselors, an incentive payment to the adolescent to participate, and the cost for using staff at each site, were also included in our calculation of total treatment cost. Indirect costs, including time and cost of traveling to the clinic, were excluded from this analysis.

Costs per unit of service were estimated in the following

Table 1
Key assumptions of cost-effectiveness analysis

Variable	Value (range)	Reference
Efficacy of IPT	.85 (.75–.98)	19
Cost of treating active TB	\$22,500 (\$17,000–\$30,000)	17
Cost of IPT	Varies by study group and whether 6-month IPT is completed	Current study
TB cases per 100,000	250 (120–560)	20
TB case fatality rate	.0045–.16 (varies with age)	17
All-cause mortality rate per 100,000	19–15,476 (varies with age)	National Center for Health Statistics, 1999 mortality tables
Hepatotoxicity of IPT	.0008 (age <35 years, started IPT) .0012 (age <35 years, completed IPT)	21
Hepatitis fatality rate	.002	21
Cost of treating IPT-induced hepatitis	\$11,250 (\$8,500–\$15,000)	Authors' assumption
QALY – healthy	1.00 (.95–1.00)	Authors' assumption
QALY – positive skin test, but incomplete IPT	.90 (.80–.95)	Authors' assumption
QALY – Active TB	.50 (.20–.90)	Harvard Center for Risk Analysis
QALY – IPT-induced hepatitis	.75 (.75–.90)	Harvard Center for Risk Analysis
Discount rate	.03 (.00–.07)	

\$30,000. Employment status was defined using two categories. Adolescents who were students and not working were defined as not working; all other adolescents, including those working full or part time and all nonstudents, were defined as working.

Baseline self-reported overall health status was recorded as excellent, good, fair or poor. Adolescents were also asked how difficult it was to get to the clinic: easy, somewhat easy, somewhat difficult, and very difficult. Responses were collapsed into two categories: difficult and not difficult/somewhat difficult. Adolescents were also asked how long it took them to see a nurse during their baseline visit, measured in minutes.

Living arrangement was categorized into three groups: adolescents who lived with both of their natural parents; adolescents who lived with one natural parent; and adolescents who lived with no natural parents.

Analytic methods

In separate analyses, we found that adolescents who were Asian, born outside the United States, and younger than 15 years of age were more likely to complete IPT [13]. In this study, we first examined a multivariate logistic regression to predict the likelihood of completing IPT. Then, we conducted a multivariate linear regression analysis with total treatment cost as our outcome variable and the key independent variables described above. We controlled for the effect of the independent variables on completion rates by using predicted completion as an independent variable in the model, with cost as the dependent variable. The purpose of this multivariate analysis was to determine if costs varied within treatment groups after controlling for factors that significantly affected compliance. Because total treatment costs were not highly skewed, ordinary least squares anal-

ysis produced normally distributed errors without transformation of the dependent variable.

Cost-effectiveness analysis

To assess the cost-effectiveness of the three interventions relative to usual care, we developed a five-stage Markov model, shown in Figure 1. Markov models are appropriate for analyzing data where study participants can transition to different health care states over time. The base case was an adolescent aged 15 years in the UC group with a positive Mantoux (i.e., TB skin) test. This model was used to estimate the lifetime TB-related costs and health benefits, measured as quality-adjusted life years (QALYs), for study participants in each treatment group relative to usual care, and is a revised version of previous Markov models that have been used to examine IPT for treatment of LTBI [17,18]. The key assumptions for this model are shown in Table 1, along with references for assumptions obtained from external sources [17,19–22]. IPT treatment costs were obtained directly from this study, including costs for those who completed therapy in each treatment group as well as costs for those who failed to complete the 6-month IPT. The Markov model was analyzed using 1-year transition states run for 100 cycles, until everyone in the hypothetical cohort died. Costs and benefits were discounted in each time period using a 3% discount rate.

The cost-effectiveness analysis was conducted from a societal perspective, so we attempted to capture total lifetime TB-related health care costs. Cost-effectiveness ratios were calculated only for treatment groups that had a statistically significant higher IPT completion rate than observed in the usual care group. One-way sensitivity analyses were performed for each of the key assumption variables shown in using the ranges specified. To confirm the results of the

Table 2
Descriptive statistics for adolescent study population

	Total		Peer Counselor		Contingency Contracting		Combined Peer / Contingency		Usual Care	
	n = 794		n = 199		n = 203		n = 197		n = 195	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Income										
Less than \$10,000	488	61.5%	130	65.3%	115	57.0%	119	60.4%	124	63.6%
\$10,001–\$15,000	254	32.0%	56	28.1%	73	36.0%	65	33.0%	60	30.8%
\$15,001–\$30,000	49	6.2%	12	6.0%	15	7.4%	12	6.1%	10	5.1%
Greater than \$30,001	3	.4%	1	.5%	0	0.0%	1	.5%	1	.5%
Gender										
Male	408	51.4%	103	51.8%	101	49.8%	103	52.3%	101	51.8%
Female	386	48.6%	96	48.2%	102	50.3%	94	47.7%	94	48.2%
Student status										
Student only, not working	620	78.1%	153	79.9%	165	81.3%	147	74.6%	155	79.5%
Other	174	21.9%	46	23.1%	38	18.7%	50	25.4%	40	20.5%
U.S.-born										
No	629	79.3%	157	78.9%	163	80.3%	159	81.1%	150	77.9%
Yes	164	20.7%	42	21.1%	40	19.7%	37	18.9%	45	23.1%
Self-rating of overall health										
Excellent	172	21.7%	35	17.6%	39	19.2%	54	27.4%	44	22.6%
Good	451	58.8%	111	55.8%	126	62.1%	102	51.8%	112	57.4%
Fair	156	19.6%	49	24.6%	33	16.3%	38	19.3%	36	18.5%
Poor	15	1.89%	4	2.0%	5	2.5%	3	1.5%	3	1.5%
Difficulty in getting to clinic										
Very difficult	153	19.3%	28	14.1%	44	21.7%	42	21.3%	39	20.0%
Not/somewhat difficult	641	80.7%	171	86.0%	159	78.3%	155	78.7%	156	80.0%
Living arrangement										
Both natural parents	356	44.8%	85	42.7%	93	45.8%	92	46.7%	86	44.1%
One natural parent	305	38.4%	78	39.2%	74	36.5%	70	35.5%	83	42.6%
Other	133	16.8%	36	18.1%	36	17.7%	35	17.8%	26	13.3%
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total cost	\$286	\$77	\$277	\$37	\$326	\$67	\$341	\$63	\$199	\$43
Completion rate	77.2	1.5	75.4	3.1	73.9	3.1	83.8	2.6	75.9	3.1
Age	15.4	1.9	15.3	1.8	15.5	1.84	15.3	1.92	15.4	1.9
Length of time to get to clinic (minutes)	24.1	17.9	22.5	15.7	23.6	20.2	25.3	18.8	25.1	16.6
Length of time waited to see a nurse (minutes)	29.0	31.9	26.7	28.3	30.3	34.7	26.6	27.3	32.4	36.1

simple Markov model, we also performed a Monte Carlo microsimulation using 10,000 trials, and calculated the 95% confidence ellipsoid for the scatterplot of incremental cost-effective ratios (ICERs) produced from this microsimulation [23]. All cost-effectiveness analyses were conducted using TreeAge Pro 2006 Healthcare software (Williamstown, MA).

Results

The characteristics of the adolescents were relatively consistent across the four groups (Table 2). The average age of the adolescents was 15 years and 4 months, and equal proportions of males and females participated in the study

(51.4% male and 48.6% female). The majority of adolescents were not born in the United States (79.3%) and came from families whose annual household income was less than \$10,000 (61.5%). Most adolescents lived with both natural parents (44.8%) or at least one natural parent (38.4%), and the majority were full-time students who did not work (78.1%).

When asked how they would rate their overall health, 58.8% of the adolescents rated their health as “good” and 1.9% rated their health as “poor.” When asked how difficult it is to get to the clinic, only 19.3% reported that it was very difficult to get to the clinic, whereas the majority (80.7%) reported that it was easy, somewhat easy, or somewhat difficult to get to the clinic. The average length of time it

Table 3
Average utilization and treatment costs of adolescents, by study group and completion of isoniazid preventive therapy

	Peer counselor		Contingency contracting		Combined peer/contingency		Usual care	
	Completed IPT (n = 150)	Did not complete IPT (n = 49)	Completed IPT (n = 150)	Did not complete IPT (n = 53)	Completed IPT (n = 165)	Did not complete IPT (n = 32)	Completed IPT (n = 148)	Did not complete IPT (n = 47)
Number of visits	6.01 (.43)	2.90 (1.40)	6.01 (.70)	2.81 (1.54)	5.99 (.79)	2.84 (1.44)	6.04 (.78)	3.04 (1.41)
Number of chest X-rays	1.03 (.18)	.98 (.14)	1.03 (.20)	1.02 (.24)	1.00 (.11)	1.06 (.25)	1.03 (.26)	1.04 (.20)
Broken appointments	1.42 (1.52)	2.65 (1.90)	1.53 (1.44)	2.74 (1.87)	1.81 (1.69)	2.65 (1.74)	1.61 (1.82)	2.45 (1.47)
Total treatment costs	\$289.77 (\$21.26)	\$237.31 (\$45.27)	\$351.75 (\$46.17)	\$254.30 (\$64.81)	\$355.89 (\$47.40)	\$261.57 (\$75.46)	\$212.33 (\$33.52)	\$158.72 (\$44.62)

Notes: Standard deviations in parentheses. Costs for individual services calculated using the 1999 Medicare Fee Schedule for services for which CPT codes were available, and using actual expenses for services without CPT codes (e.g., contingency contract incentives).

took for the adolescent to get to the clinic was 24 minutes and the average length of time he/she waited to see a nurse was 29 minutes.

The average total cost of treatment across the four groups was \$286, but the average cost varied considerably among groups (Table 2). As expected, the combined peer counselor/contingency (PC + CC) contracting group had the highest total cost (\$341), followed by the contingency contracting (CC) group (\$326), the peer counselor (PC) group (\$277), and the usual care (UC) group (\$199). The average costs in each of the four groups were significantly different from each other at the $p = .001$ level. Our estimate of the total treatment cost for usual care is comparable to the other major published study on the costs of LTBI control [17]. The cost of the incentives offered to adolescents in the CC group and the PC + CC group averaged almost \$60.

Although the PC + CC group had the highest total cost, it also had the highest rate of program completion (83.8%), followed by the UC group (75.9%), the PC group (75.4%), and the CC group (73.9%) (Table 2). The difference between the PC + CC group and the UC group was nearly significant at the 5% level ($p = .051$, two-tailed test). The differences in average cost between adolescents who completed IPT and those who failed to complete IPT were rather large, as shown in Table 3. These cost differences were used in the cost-effectiveness model shown in Figure 1.

Because only the PC + CC group had a significantly higher completion rate compared with the UC group, we limited our cost-effectiveness analysis to a comparison of these two groups. The results of our Monte Carlo micro-simulation analysis showed that, relative to the UC group, the PC + CC group produced better lifetime QALYs per person (.1962) at a slightly higher lifetime cost (\$41) (Table 4), indicating that this intervention had an incremental cost-effectiveness ratio (ICER) of \$209 per QALY. These findings were consistent for all one-way sensitivity analyses performed using the ranges shown in Table 1. The analysis of the scatterplot of the 10,000 ICERs produced in the Monte Carlo simulation indicated that in 89.75% of the trials, costs were higher in the PC + CC group without any additional improvement in QALYs (i.e., $IC > 0$, but $IE = 0$). For the remaining 10.25% of trials, costs and QALYs were higher in the PC + CC group, but in all trials, the ICER was less than \$50,000, which is a common willingness-to-pay threshold.

Our logistic regression analysis of the factors associated with successful completion of IPT indicated that the odds of completing care is reduced by 55% when a child lives with one natural parent, compared with both natural parents (odds ratio [OR] .454, 95% confidence interval [CI] .290–.711), and by 67% when a child lives with no natural parent, compared with both natural parents (OR .372, CI .189–.565), controlling for study group and other factors. The odds of completing care are reduced by 48% when the adolescent is born in the United States, compared with

Table 4
Summary of cost-effectiveness analysis

Group	Effectiveness in QALYs	Incremental effectiveness (IE) in QALYs	Average lifetime TB-related costs	Incremental cost (IC)	Average CE ratio	Incremental CE ratio (ICER)
UC	24.2006	–	\$767	–	\$36	–
PC + CC	24.3968	.1962	\$808	\$41	\$38	\$209

CE = cost effectiveness; UC = usual care; PC + CC = peer counselor and contingency contracting.

Using 10,000 Monte Carlo microsimulation trials, 89.75% of cases had IC > 0 but IE = 0; 2.96% had IC < 0 and IE > 0; 7.23% had IC > 0, IE > 0, and ICER < 50,000; and .06% had IC < 0 and IE < 0.

adolescents born in other countries (OR .516, CI .330–.805) [13]. After controlling for the impact of these factors by including predicted completion in a model of treatment costs, we found no other significant relationship between our study variables and total treatment costs, except for treatment group. We conclude, therefore, that although there are important factors associated with completion of IPT, controlling for these factors eliminates the impact of these factors on total treatment costs.

Discussion

For children and adolescents, incentives can serve as a positive reinforcement when trying to get them to complete care that is critical for their health. In this study, we were interested in understanding the costs and cost-effectiveness of an incentive-based program that can enhance adolescent completion of IPT for treatment of LTBI.

Our findings support the idea that incentives are successful in improving the overall completion rate of care, but only when accompanied by another program such as peer counseling. When incentives are provided alone with no other form of therapy, then the overall completion rate of the care is not improved and may actually be less than that of other programs such as peer counseling and usual care, although another recent study has shown that coaching can be effective in improving adherence among Latino adolescents [24]. Other research suggests that directly observed therapy, in which individuals with LBTI take their medication in front of a health professional, can also improve adherence; the cost-effectiveness of this strategy has not been evaluated, however [25].

More times than not, incentives are associated with a monetary cost, thus making an incentive-based program more costly than a non-incentive-based program. Our study finds that either incentives alone or incentives as part of a peer-counseling program are more costly than usual care or peer counseling programs with no incentives. However, when controlling for other variables, there is only a slight difference in cost between an incentive-only program vs. a program that combines incentives and peer counseling.

In terms of cost-effectiveness, our main question of interest was whether or not greater cost of incentives is a

cost-effective strategy in trying to get adolescents to adhere to a TB control program. Several previous studies have demonstrated the cost-effectiveness of IPT [17,19,26–29]. Our findings do, in fact, support the conclusion that incentives when combined with peer counseling are a cost-saving strategy to enhancing care completion, resulting in better outcomes at an average cost of \$209 per QALY.

In summary, programs that are currently in place that target children or adolescents may want to consider adding peer education counseling and tangible incentives to the program's protocol to increase overall care completion rates. As shown in this study, although the overall program cost will increase by adding incentives, so too will the overall completion of care. Ultimately, despite the higher cost, a higher completion rate will prevent LTBI cases converting to active tuberculosis and result in cost-effective improvements in quality-adjusted life expectancy.

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