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RESEARCH ARTICLE

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Cost of Tuberculosis Relapse in Yemen: A Nested Case-Control Study

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Abstract

Background: The economic burden of tuberculosis (TB) in Yemen is enormous. Little empirical information is available about TB relapse-related cost incurred by government for treating relapse patients. **Objective:** The present study aims to estimate the direct cost of TB relapse from the government's perspective. **Materials and Methods:** In the current study, a pharmacoeconomic analysis was conducted using the cost-of-illness method, which determines the direct and indirect costs of a specific disease. Forty-four relapse cases and 176 controls were included in the analysis. **Results:** T-test and Mann–Whitney U test showed a significant difference in mean and median of direct medical cost components. T-test also shows a significant difference in mean of the total relapse cost between males and females ($P < 0.05$). The cost incurred by the government to treat one relapse case (US$92.31) was about three times more for that of treating a non-relapse (US$35.02), with an extra cost for a relapse case of US$57.29. It is estimated that cumulative costs for treating relapse cases ($n = 5764$) reported through 1996-2010 was US$532,074.84. **Conclusion:** Study findings concluded that the cost to the government for the management of tuberculosis patients is substantial and inflicts considerable economic burden on the overall health care system of Yemen. The cost could be reduced by incorporating cost-effective strategies in tuberculosis control to prevent relapse.

Key words: Cost, Nested, DOTs, Relapse, Tuberculosis, Yemen.

INTRODUCTION

Tuberculosis is a disease that kills nearly two million people at their most economically productive age (15-54 years) yearly. On average, a TB patient loses three to four months of work time because of the illness, which is equivalent to approximately 20% to 30% of the annual household income and about 15 years of income is lost because of premature death.[1] In addition to devastating economic costs, TB imposes indirect negative consequences; women with TB are unable to practice their essential responsibilities

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for their families. Furthermore, a person with TB can be rejected by their community, friends and even family. A tuberculosis patient's income loss increases as health care is sought, prompting household members to change their strategies to reduce total family expenses. Thus, the children could miss educational opportunities, food intake could decrease and the family might need to sell some of their assets and borrow money from others.[2,3] Tuberculosis robs people of opportunities, limits their choices and ultimately slows down national development. Cost-of-illness studies measure the economic burden of a disease and estimate the maximum amount that could potentially be saved or gained if a disease was to be eradicated.[4] Knowledge of the costs of an illness can help policymakers to prioritize care and disease prevention. In cost-of-illness studies, three different types of costs are usually mentioned namely, direct, indirect and intangible costs.[4] Cost-of-illness studies can show the government, the financial impacts of diseases on public health programmes.[5,6] Tuberculosis is considered as one of the major public health problems in Yemen and is estimated to be the fourth cause of death. It costs the country wasting a lot of resources; relapse of TB could complicate this situation and hamper TB control and success of the National TB control programme (NTCP). Through quantifying of the cost of tuberculosis relapse, a reduction on the economic burden of tuberculosis in the country could be achieved. Through providing evidence on possible cost savings by relapse prevention, the findings will provide policy makers and planners with strong argument to justify continued allocation of resources for the TB programme. Furthermore, the findings could provide baseline information for further monitoring of tuberculosis relapse in Yemen. The economic effect of TB relapse is not well known in Yemen. The present study aims to estimate the direct cost incurred for treating relapse patients from the government's perspective.

MATERIALS AND METHODS

Study design

A prospective nested case-control study was conducted to identify the risk factors of relapse among tuberculosis patients. By the end of the follow-up period (15-03-2011), all the relapse cases were identified from the tuberculosis registry. For each confirmed relapse case, four controls from those who successfully completed initial treatment and did not relapse were randomly selected. Using the data derived from the follow-up of the original study cohort, the pharmacoeconomic analysis to estimate the direct medical cost (i.e. health care resources consumed for the treatment and management of disease) of TB relapse from the government's perspective was conducted. Direct medical cost components were the cost of anti-TB drugs, laboratory tests, chest X-ray examinations and health care staff time.[3,7] The direct non-medical cost was excluded because of the different sources of funding.

Study Area and Population

The study was conducted at the health centres where the TB units are exist throughout ten governorates of Yemen. The study population was a cohort of smear positive pulmonary TB (PTB) patients registered for DOTS between July 2008 and June 2009. Patients who completed treatment regimen and declared as cured and aged 15 years old and above were included as subjects for this study, while all smear negative PTB, extra-PTB and children less than 15 years old were excluded. The sample size consisted of 44 relapses and 176 controls (non-relapse) who were randomly selected using the SPSS computerized sampling procedure at a ratio of 1:4 from the list of non-relapse patients (n=730). Demographic and socioeconomic information were obtained from the patient treatment cards, the TB registry and the questionnaire used in the original study on TB relapse predictors.

Cost analysis

Unit price of the items used in treatment is shown in Table 1. To estimate direct medical cost, the cost of anti-TB drugs, laboratory tests and chest X-ray examinations as well as the cost of health care staff time were calculated.

Cost of anti-TB drugs

The cost of anti-TB drugs was calculated based on the price of a tablet multiplied by the number of tablets taken per day and by the number of days of the treatment period, which took eight months for the PTB patients.

Cost of laboratory test

The amount of items used in millilitres/milligrams was multiplied by the cost of one millilitre/milligram and by the number of tests (six tests during the treatment regimen) to calculate the cost of AFB test for TB patients.

Cost of X-ray examinations

The costs of film and reagent were calculated and multiplied by the number of films used for each patient.

Cost of health care staff time

Table 1: Unit price of the items used in treatment.

Item	Unit	Unit Price US$
RHZE 150/75/400/275 mg	Tablet	0.06
EH 400/150 mg	Tablet	0.03
RHE 400/150 mg	Tablet	0.04
Streptomycin 1 g	Vial	0.10
Disposable syringe	Syringe	0.05
Water for injection	Ampoule	0.04
Glass Slides	slide	0.03
Sputum cup	Cup	0.04
Fuchsine	Milligram	3.60
Methylene Blue	Milligram	0.40
Sulfuric acid	Millilitre	0.02
Phenol crystalline	Milligram	0.08
Xylene	Millilitre	0.01
Ethanol	Millilitre	0.01
Immersion Oil	Millilitre	0.11
DOTs Cards	Card	0.09
Green Cards	Card	0.15
Exam. Sputum Sheets	Sheet	0.05
X-ray film	Film	0.79

R= Rifampicin ; H= Isoniazed; Z = Pyrazinamide; E =Ethambutol; S =Streptomycin

Health care staff includes all workers in different TB diagnosis and treatment sections (physician, laboratory technician, primary health worker/DOTS supervisor and X-ray technician). The cost can be obtained by calculating the time spent of a health worker on each patient.[8] The salary per minute of a health worker is then multiplied by the time in minutes used to attend to each patient. A researcher followed ten patients for each section and then calculated the time spent for each patient in each section without informing the health worker to validate the collected data. The mean of time spent (reported and actual) by each group of health care staff were compared. T-test did not show any significant differences (p>0.05) among the compared means of time spent (reported *versus* actual). All costs were calculated in Yemeni currency (YR) and converted to the United States currency based on the 2008 exchange rate of US$1.00=YR199.5.

Statistical analysis

Descriptive and inferential statistics were used in the present study. All findings were described in terms of frequencies and percentages. The mean and median of the different components of the direct medical cost were also reported. T-test or Mann-Whitney U test was used to evaluate the differences in means or medians of the different components' cost and the total direct medical cost between the relapse and non-relapse groups. Data were analyzed using SPSS software package (Version 15.0, SPSS Inc, Chicago, IL) at significance level of 0.05. Microsoft Excel worksheet (Windows 7) was used to perform calculations related to the cost of anti-TB drugs, laboratory tests, chest X-rays and health care staff time. The research was approved by ethical committee of medical research in Ministry of public health and population. Written consent was obtained from the patients explaining the study objectives.

RESULTS

The cohort of new smear positive PTB registered for DOTS from July 2008 to June 2009 consisted of 955 patients. Out of this number, 838 (87.8%) patients actually completed the questionnaire, among whom only 814 were identified as the cohort for follow-up. A descriptive analysis of the study cohort showed that approximately 90% of the respondents were at their most economically productive age with a mean of 32.1 (±13.6 SD) years old. By the end of the follow-up period, a total of 44 cases who relapsed within 12 months after completion of treatment were identified from the TB registry. Accordingly, a total of 176 controls were randomly selected from those who had no relapse (n=730). The baseline characteristics of the investigated sample (n=220) are described in Table 2.

Cost of TB relapse

The analyzed cost was a direct medical cost. Descriptive analysis of the direct medical cost of the health care staff time and the total direct medical cost and its components from the government's perspective is presented below.

Analysis of the Cost of health care staff time

In terms of the time criterion, the analysis showed that the primary health workers represented the highest cost with 49.5% and 52.3%, followed by the laboratory technicians with 39.5% and 37.4% and then by the physicians with 9.1% and 8.6% for the non-relapse and relapse patients, respectively. The X-ray staff represented the lowest cost with 1.8% and 1.7% for the non-relapse and relapse patients, respectively. Table 3 shows the total expenditure of the health care staff as well as the proportion (%) of each group expenditure.

Analysis of the total direct medical cost

Table 4 shows the total direct medical cost and the proportion of each component expenditure as well as the

Table 2: Baseline characteristics of the study sample (n=220)

Variable	Total n (%)	Cases (relapse) n (%)	Controls (Non-relapse)	P value n (%)
Gender				
Female	92 (41.8)	12 (27.3)	80 (45.5)	
Male	128 (58.2)	32 (72.7)	96 (54.5)	.029*
Age				
≥45	25 (11.4)	5 (11.4)	20 (11.4)	NS
<45	195 (88.6)	39 (88.6)	156 (88.6)	
Literacy Status				
Literate	139 (63.2)	20 (45.5)	119 (67.6)	.006*
Illiterate	81 (36.8)	24 (54.5)	57 (32.4)	
Marital Status				
Married	133 (60.5)	29 (65.9)	104 (59.1)	NS
Unmarried	87 (39.5)	15 (34.1)	72 (40.9)	
Employment				
Employed	91 (41.4)	11 (25.0)	80 (45.5)	.014*
Unemployed	129 (58.6)	33 (75.0)	96 (54.5)	
Smoking				
No	179 (81.4)	34 (77.3)	145 (82.4)	NS
Yes	41 (18.6)	10 (22.7)	31 (17.6)	
Khat Chewing				
No	104 (47.3)	16 (36.4)	88 (50.0)	NS
Yes	116 (52.7)	28 (63.6)	88 (50.0)	
Cavitations				
No	151 (68.6)	16 (36.4)	135 (76.7)	<0.05*
Yes	69 (31.4)	28 (63.6)	41 (23.3)	
Compliance†				
Yes	166 (75.5)	20 (45.5)	146 (83.0)	<0.05*
No	54 (24.5)	24 (54.5)	30 (17.0)	
Diabetes ‡				
No	199 (90.5)	35 (79.5)	164 (93.2)	.010**
Yes	21 (9.5)	9 (20.5)	12 (6.8)	

NS=Not Significant; † Pearson Chi-square; ‡ Fisher's exact test

Table 3: Analysis of the cost of health care staff time

Health Personnel	Total cost for controls (US$)	%	Total cost for cases (US$)	%
Physician	0.93	9.1	1.86	8.6
Laboratory technician	4.07	39.5	8.14	37.4
Primary health worker	5.09	49.5	11.37	52.3
X-ray technician	0.19	1.8	0.38	1.7
Total	10.28	100%	21.75	100%

mean and the median of the total direct medical cost and its components/health services. The drug expenditures amounted to more than half of the total direct medical cost of health services for both types of patients. The drug expenditures represented the highest cost with 59.0% and 67.6%, followed by the health staff with 29.4% and 23.6%, and finally by the chest X-ray with 7.4% and 5.6% for the non-relapse and relapse patients, respectively. The laboratory test expenditures represented the lowest cost with 4.2% and 3.2% for the non-relapse and relapse patients, respectively.

Table 4: Analysis of the total direct medical cost

A. The total direct medical cost and the proportion (%) of its component

Item	Total cost for controls (US$)	%	Total cost for cases (US$)	%
Cost of Drugs	20.68	59.0	62.44	67.6
Cost of Lab. Test	1.48	4.2	2.96	3.2
Cost of X-ray examinations	2.58	7.4	5.16	5.6
Cost of Health Staff	10.28	29.4	21.75	23.6
Total	35.02	100%	92.31	100%

B. Average of the total direct medical cost and its components

Component	Controls (US$)	Cases (US$)
Anti-TB drugs		
Mean (SD)	20.68 (0.37)	62.44 (1.43)
Median (IQR)	20.88 (20.54-20.88)	63.11 (61.88-63.44)
Laboratory tests		
Mean (SD)	1.48 (0.00)	2.96 (0.00)
Median (IQR)	1.48 (1.48-1.48)	2.96 (2.96-2.96)
X-ray examinations		
Mean (SD)	2.58 (0.00)	5.16 (0.00)
Median (IQR)	2.58 (2.58-2.58)	5.16 (5.16-5.16)
Health care staff time		
Mean (SD)	10.28 (0.07)	21.75 (0.32)
Median (IQR)	10.31 (10.31-10.31)	21.85 (21.76-21.85)
Total		
Mean (SD)	35.02 (0.42)	92.33 (1.65)
Median (IQR)	35.25 (34.95-35.25)	93.00 (91.86-93.42)

The analysis showed that the average cost of each medical component service as well as the total direct medical cost incurred by the government to treat one relapse case are higher than the cost incurred to treat a non-relapse. The average total direct medical cost was US$92.31 and US$35.02 for relapse and non-relapse, respectively, with an extra cost for a relapse case of US$57.29. However, the total extra direct medical cost requested for treating 44 relapse patients found to be US$2,520.76 (US$57.29/patient), whereas the overall direct medical cost requested was US$4,061.64 (US$92.31/patient). In addition, it can be concluded that government spent about US$17,989.06 extra direct medical cost and US$28,985.34 as overall direct medical cost for treating 314 relapse cases reported in 2009. However, it makes sense to conclude that a cumulative extra and overall direct medical costs for treating relapse cases (n=5764) reported through 1995 till 2009 were about US$330,219.56 and US$532,074.84, respectively. Meanwhile, the cost of new cases (n=62480) reported at the same period was US$2,188,049.60.

Inferential analysis was performed to determine the difference in the mean and median of the obtained costs between relapse and non-relapse groups. T-test analysis showed a significant difference in the mean cost of laboratory tests and chest X-ray examinations ($p<0.001$). However, Mann–Whitney U test showed a significant difference among the median cost of anti-TB drugs, health care staff time and the total direct medical cost ($p<0.001$). Table 5 summarized the inferential analysis of the total direct medical cost and the cost of its components between relapse and non-relapse groups. T-test analysis was also performed to determine the difference in mean of total cost of relapse by gender. The test showed a significant difference in the mean cost between males and females ($p<0.05$), Table 6 summarized the results.

DISCUSSION

The social and economic burden of TB follows its characteristic age distribution, in which TB affects all age groups but has the greatest impact on productive adults[9] Adults aged 15 to 54 years old are known to be the most

Table 5: Inferential analysis of direct medical cost for non-relapse and relapse patients

Component	Statistic	Controls	Cases	P value
Drugs	Median (IQR)	20.88 (20.54-20.88)	63.11 (61.88-63.44)	< 0.001‡
Laboratory test	Mean (SD)	1.48 (0.00)	2.96 (0.00)	< 0.001†
X-ray examinations	Mean (SD)	2.58 (0.00)	5.16 (0.00)	< 0.001†
Heath Staff	Median (IQR)	10.31 (10.31-10.31)	21.85 (21.76-21.85)	< 0.001‡
Total cost	Median (IQR)	35.25 (34.95-35.25)	93.00 (91.86-93.42)	< 0.001‡

NS=not significant; † t-test; ‡ Mann-Whitney test

Table 6: Inferential analysis of the total cost of relapse by gender

Component	Statistic	Males	Female	P value
Total Cost	Mean (SD)	97.94 (3.62)	95.28 (3.13)	< 0.05†

† t-test

economically productive individuals and they are the parents on whom the survival and development of children are dependent. Thus, TB has the potential to impede the development of both an individual and the society.[10] In the current study, approximately 90% of respondents were between 15 and 54 years old which is consistent with the estimation of WHO that TB affects the most economically productive age group. The pharmacoeconomic analysis in this study was conducted using the cost-of-illness method which determines the direct and indirect costs of a specific disease.[11] In the present study, the average cost was considered in all calculations of TB treatment regimens because it best reveals the real expenditure. Thereafter, the significant difference in the mean and median of the different components of the direct medical cost and the total direct medical cost between the relapse and the non-relapse patients was investigated. The present study observed that the large proportion of the total direct medical cost of health services corresponded to the cost of anti-TB drugs with 59.0% and 67.6%, which were equivalent to US$20.68 and US$62.44 for non-relapse and relapse patients, respectively. The percentage of the cost of anti-TB drugs was higher in relapse cases compared with that in non-relapse cases because the treatment period for relapse patients was longer. The relapse patients undergo two treatment regimens (Category I and Category II). A higher cost finding (59.0%) was discovered in the comparison of the cost of anti-TB drugs in this study with those of studies in Malaysia, India, Bangladesh, Ethiopia, Tanzania and Uganda,[3, 7, 8, 12–14] where the percentages of the cost of anti-TB drugs relative to the total costs of illness expenditures were 32.4%, 25%, 37.9%, 19%, 44%, and 37%, respectively. The high percentage of anti-TB drug cost in our study could be due to the fact that TB programme in Yemen performed only the AFB and chest X-ray tests for the registered patients, whereas other studies included several other tests. The current study found that costs of the laboratory tests per patient were US$1.48 (4.2%) and US$2.96 (3.2%) for non-relapse and relapse, respectively. Elamin *et al*. stated that the laboratory tests per treated patient incurred a higher cost of US$28.53, which constituted 15.1% of the total cost of government health services. Islam *et al*. showed a comparable cost for the laboratory examination of US$9.6, which constituted 3.7% of the total cost of the health services. The current study found that the costs associated with chest X-ray services per patient were US$2.58 (7.4%) and US$5.16 (5.6%) for non-relapse and relapse, respectively. In comparison, the previous study conducted by Elamin *et al*. found that the cost of chest X-ray was high (US$28.63), it constituted 15.1% of the total cost of health services. The low proportion of chest X-ray cost in this study could be due to the difference in the average number of X-ray films used per patient. The average number of films used in the Malaysian study,[3] was between five and six films, whereas it was only two films in the present study. However, Wyss *et al*. found that only US$1.40 was paid for X-ray, which constituted 1.6% of the total provider cost. The total cost of the health services in the present study was US$35.02 and US$92.31 per patient for the non-relapse and relapse groups, respectively. In the current study, the total direct medical cost of non-relapse patients was comparable to that of the Indian study,[7] which identified the total direct medical cost for non-relapse at US$35.00. However, the total direct medical cost of relapse patients in the current study was higher than that of a previous Indian study (US$92.31 versus US$42.00). A comparable finding was revealed in two other studies conducted in India and Pakistan.[15,16] In the Indian study, the cost of health services was US$46.00, whereas in the Pakistan study, the cost amounted to US$50.26. On the other hand, very high expenditures were determined in the Haitian study,[17] which evaluated the total direct medical cost per PTB patient to be US$432.00. The Malaysian,[3]

Ethiopian,[12] Brazilian,[18] and Tanzanian [19] studies reported that the total direct medical cost of treating a PTB patient was US$95.60, US$189.50, US$103.00, and US$115.30, respectively. However, the study conducted in Bangladesh [8] showed that the direct medical cost of PTB patient was lower at US$77.00. Moreover, the reported cost represented twice the cost found in the present study at US$35.02. The differences in the results of the present and other related studies could be due to the exclusion of some direct medical cost components, such as overhead and hospitalization. The current study found a significant difference in the mean cost between males and females; it could be due to the difference in compliance between them.

To our knowledge this study is the first of its kind in Yemen and has definitely contributed significant information to the policy makers, health care managers and practitioners; this is in spite of the fact that some of the costs were excluded. Based on the exploring analysis of the study sample (n=220) characteristics, the relapse subjects compared to non-relapse were recognized to be illiterates, unemployed, non-compliants, diabetics and had a cavitary tuberculosis. From this point of view, the findings of our study could have several programme implications. First, there is a need for a course of action to help unemployed patients including free service and increasing a health education among TB patients, both of which would be expected to lead to a reduction in non-compliance, thus reducing of a relapse risk and a related economic burden. Second, the study findings showed a significant association between diabetes and TB relapse, to reduce the eventuality of this association, recently, WHO recommends bi-directional screening in TB and diabetes patients. Based on this recommendation all diabetes patients should be counselled on the risk of TB and screened for TB on regular basis. In the same context, the TB patients should be screened for diabetes to reduce the occurrence of TB relapse among the cured patients. Third, in the randomized controlled trial mentioned, the relapse rate for a 6-month regimen containing rifampicin throughout (2RHZE/4HR) was half that for 2RHZE/6HE (5%).[20] Therefore, changing from the current standard regimen to one with rifampicin in the continuous phase could reduce the relapse rate, especially among the patients with cavitary TB. Based on the previous evidence, it can be recommended to use rifampicin-based regimens in treatment cavitary tuberculosis in Yemen TB programme.

Strengths and Limitations of the Study

The main strength of the study is that costing was conducted prospectively alongside a nested-control study on the risk factors of TB relapse. Although the exclusion of non-medical cost was justified, it is still a limitation in this study.

CONCLUSION

The study findings concluded that the cost to the government for the management of TB patients is substantial and inflicts considerable economic burden on the overall health care system of Yemen. The partial pharmacoeconomic analysis showed that the estimated average of total direct medical cost incurred by the government per case was US$35.02 and US$92.31 for non-relapse and relapse, respectively, with an extra cost for a relapse case of US$57.29. Based on the number of relapse cases (1996-2010), the Yemen government is expected to spend about US$532,074.84 for treating relapse cases. The cost of anti-tuberculosis drugs constitutes the highest proportion of the total direct medical cost with 59.0% and 67.6% for non-relapse and relapse groups, respectively. The cost could be reduced by applying an alternative treatment design. The health care policy makers and planners must consider TB control as high priority and incorporating cost-effective strategies in TB control such as offering free service for unemployed patients, reinforcing health education activities, smoke cessation support, bi-directional screening in TB and diabetes patients, using of rifampicin-based regimens in treatment cavitary tuberculosis and reinforcing of the DOTS strategy should be adopted. All these are expected to prevent TB relapse, thus reducing patient and societal expenditures as well as saving limited government resources. Although the exclusion of non-medical cost was justified, a further study on the overall cost might be beneficial even if the study will be conducted in the selecting settings where all the costs recovered by government.

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CONFLICT OF INTEREST

The authors would like to declare that there is no conflict of interest

ABBREVIATIONS USED

TB: Tuberculosis; US$: United state dollar; DOTs: Directly Observed Treatment, Short-course; NTCP: National TB control programme; PTB: Pulmonary tuberculosis; AFB: Acid- Fast Bacilli;SD: Standard deviation; IQR: Interquartile range; WHO: World Health Organization; EMRO; Eastern Mediterranean Regional Office (World Health Organization).

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