ECONOMIC AND HEALTH RELATED QUALITY OF LIFE EVALUATION OF TUBERCULOSIS PATIENTS IN YEMEN

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ECONOMIC AND HEALTH RELATED QUALITY OF LIFE EVALUATION OF TUBERCULOSIS PATIENTS IN YEMEN

by

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LIST of ABBREVIATIONS

AFB: Acid Fast Bacilli

BCG: Boston Consulting Group

COPD: Chronic Obstructive Pulmonary Disease

DOTS: Direct Observed Treatment

DR-12: Dhingra and Rajapal Questionnaire with 12 Items

E: Ethambutol

EP: extrapulmonary TB

I: Isoniazid

HIV: Human Immunodeficiency Virus

HRQol: Health Related Quality Of Life

LTBI: latent Tuberculosis Infection

M: Mycobacterium

MDR-TB: Multidrug Resistance TB

New P. Sm+: New Pulmonary TB Smear Positive

New P. Sm+: New Pulmonary TB Smear- Negative

QoL: Quality Of Life

PTB: pulmonary TB

R: Rifampicin

RaQoL: Rheumatoid Arthritis Quality of Life

S: Streptomycin

SF-36: Short Form-36 Items

SF-12: short form-12 items

USD: United State Dollar

T: Thioacetazone

TB: Tuberculosis

TST: Tuberculin Skin Test

WHO: World Health Organization

Z: Pyrazinamide

PENILAIAN EKONOMI DAN KUALITI HIDUP BERKAITAN KESIHATAN PESAKIT TUBERKULOSIS DI YEMEN

ABSTRAK

Kajian ini bertujuan untuk mengakses aspek ekonomi dan kualiti hidup berkaitan kesihatan pesakit tuberkulosis di Yemen. Kajian berbentuk keratan lintang dan prospektif telah dijalankan dalam kalangan pesakit-pesakit tuberkulosis pulmonari dan ekstra-pulmonari yang telah didiagnosis dan dirawat di pusat TB di Sana'a, ibu kota Yemen. Data sosio-demografik, klinikal dan makmal serta jenis regimen ubat yang digunakan dalam rawatan dikumpulkan daripada pesakit TB dan rekod perubatan di pusat TB. Metodologi farmakoekonomi telah diaplikasi untuk mengira kos langsung dan tidak langsung. Pesakit diminta untuk melengkapkan soal selidik DR-12. Pesakit perlu mengisi soal selidik tersebut pada permulaan rawatan, selepas satu bulan dan diulangi pada akhir fasa rawatan intensif. Nisbah wanita kepada lelaki adalah 1.2 dan 1.6 masing-masing bagi tuberkulosis pulmonari dan ekstra pulmonari. Umur median pesakit tuberkulosis pulmonari adalah 29 dan 30 bagi pesakit tuberkulosis ekstra pulmonari. Kajian ini mendapati bahawa bilangan pesakit tuberkulosis ekstra pulmonari yang didiagnosis di hospital swasta dan klinik (41%) adalah lebih tinggi berbanding pesakit tuberkulosis pulmonari (26%). Kos-kos perubatan langsung, bukan perubatan langsung dan tidak langsung bagi TB pulmonari adalah masing-masing US 30.07, US$ 36.94 dan US$ 73.10. Manakala bagi TB ekstra pulmonari adalah masing-masing US$ 32.71, US$ 99.90 dan US$ 51.90. Kos yang ditanggung oleh pesakit TB pulmonari dan

ekstra pulmonari adalah masing-masing sekitar 76.1% dan 89.4% daripada kos keseluruhan rawatan. TB pulmonari menunjukkan skor HRQoL yang lebih buruk berbanding dengan TB ekstra pulmonari ($P<0.05$). Perbezaan yang paling besar dilihat pada dimensi yang mencerminkan simptom semasa fasa intensif. Penambahbaikan pada HRQoL kedua-dua pesakit pulmonari dan ekstra pulmonari bagi ketiga-tiga domain selepas satu bulan rawatan dan akhir fasa intensif adalah signifikan secara statistik ($P<0.001$), bagi setiap kumpulan apabila dibandingkan dengan masa awal. Secara kesimpulan, kajian ini menunjukkan bilangan wanita dan pesakit muda adalah lebih tinggi bagi kedua-dua TB pulmonari dan ekstra pulmonari. Bilangan pesakit ekstra pulmonari yang didiagnosis di hospital swasta dan klinik adalah lebih tinggi berbanding dengan pesakit TB pulmonari. Pesakit ekstra pulmonari berpendapatan bulanan lebih rendah berbanding dengan TB pulmonari. Daripada perspektif perkhidmatan kesihatan dan pesakit, kos bagi terapi TB pulmonari adalah masing-masing 23.9% dan 76.1%, manakala kos bagi TB ekstra pulmonari adalah masing-masing 10.6% dan 89.4%. Dalam kajian HRQoL, pada permulaan terapi, pesakit TB pulmonari secara signifikan mempunyai HRQoL yang lebih rendah berbanding dengan pesakit TB ekstra pulmonari. Kedua-dua pesakit TB pulmonari dan ekstra pulmonari secara signifikan bertambah baik selepas masa awal rawatan. Pesakit TB pulmonari yang bertukar bertambah baik dari segi simptom berbanding dengan pesakit TB pulmonari yang tidak bertukar.

ECONOMIC AND HEALTH RELATED QUALITY OF LIFE EVALUATION OF TUBERCULOSIS PATIENTS IN YEMEN

ABSTRACT

The study aims to assess the economic and the health related quality of life for tuberculosis patients in Yemen. A Cohort prospective study was carried out among pulmonary tuberculosis and extra pulmonary tuberculosis patients diagnosed and treated in a TB centers in Sana'a, the capital city of Yemen. Socio demographic, clinical and laboratory data and types of drug regimen used in treatment were collected from TB patients and medical records at the TB centers. Pharmacoeconomic methodology was applied to calculate direct and indirect costs. The patients were asked to complete DR-12 questionnaire. The patients was subjected to the questionnaire at onset of treatment, then after one month and finally repeated at the end of intensive phase of treatment. The female to male ratio was 1.2 and 1.6 for pulmonary tuberculosis and extra pulmonary tuberculosis, respectively. The median age for pulmonary tuberculosis patients was 29 and 30 years for extra pulmonary tuberculosis patients. This study found the extra pulmonary tuberculosis patients diagnosed in private hospital and clinics (41%) were more than pulmonary tuberculosis patients (26%). The direct medical, direct non-medical and indirect costs for pulmonary TB were US$ 30.07, US$ 36.94 and US$ 73.10, respectively. While for extra pulmonary TB, the costs were US$ 32.71, US$ 99.90 and US$ 51.90, respectively. Of the total costs of treatment, the cost for

pulmonary TB and extra pulmonary TB patients constitutes approximately 76.1% and 89.4%, respectively.

Pulmonary TB had significantly worse HRQoL score compared to extra pulmonary TB ($P<0.017$). The greatest difference was observed in the dimension reflecting symptoms, during the intensive phase. The improvement in HRQoL for both pulmonary and extra pulmonary patients for the three domains, after one month of treatment and at the end of intensive phase were statistically significant ($P< 0.001$), for each group compared to the base line. In conclusion, this research showed that, female and younger ages were higher in both extra pulmonary and pulmonary TB. The extra pulmonary TB patients diagnosed in private hospital and clinics were higher than pulmonary TB patients. The extra pulmonary have less monthly income than pulmonary TB.

From the perspectives of the health services and patients, the total cost for pulmonary TB therapy were 23.89 % and 76.11%, respectively, while the total cost for extra pulmonary TB were 10.6% and 89.4%, respectively. The cost of anti-TB drugs constitutes the highest proportion of the costs to the public health services, 38.1% and 78.0% for pulmonary and extra pulmonary TB, respectively. In HRQoL study, at the beginning of therapy, pulmonary TB patients have significantly lower HRQoL than extra pulmonary tuberculosis patients. Both pulmonary and extra pulmonary TB patients are significantly improved after onset of treatment. The converted pulmonary TB patients improved in symptoms as compared to the non converted pulmonary TB patients.

CHAPTER 1

INTRODUCTION

1.1 Overview

Mycobacterium Tuberculosis (TB) is an infectious communicable disease which is a major cause of death in the world (WHO, 2007). There are two principle kinds of TB: pulmonary TB, which usually attacks the lungs, and extra-pulmonary TB, which attacks any part of the body, such as: the lymphatic, pleura, bone and/or joint, genitourinary tract, miliary, peritoneal, meninges and/or central nervous system (CNS); and all organ systems that may be affected. Sometimes patients suffer from both pulmonary TB combined with extra pulmonary TB (Parimon et al., 2008; Sreeramareddy et al., 2008; Mario et al., 2008).

Mycobacterium Tuberculosis is most transmitted from a person with infectious pulmonary tuberculosis to others by droplet nuclei through cough, sneeze, or speak. Furthermore, having close contacts to the infected persons, intense, duration, or repeated contacts are considered among the major routes to infect with TB. Other resources include: foreign-born from endemic area with TB, residents and employees living in congregated areas, health care workers who work with severely infected patients, low-income populations, racial or ethnic minority populations, children in contact with severely infected adults, and finally persons who inject illicit drugs (American Thoracic Society, 1999; Smith and Moss, 1994; Verver et al., 2004; Palomino et al., 2007).

Extra pulmonary TB that occurs outside the lungs may spread through lymphatic or hematogenous dissemination to any tract or through coughing and swallowing to the gastrointestinal tract. Such type of bacteria may stay latent for years at a particular site before causing the illness. Nearly all organs of the body can be influenced by extra pulmonary TB; it has a wide variety of clinical manifestations; therefore making it less familiar to most of clinicians and delay of diagnosis (Beek et al., 2006; Gonzalez et al., 2003).

Extra pulmonary TB, is more often diagnosed in women and young patients; extra pulmonary tuberculosis is seen more commonly today than in the past (Mario et al., 2008; Aaron et al., 2004; Rieder et al., 1990; Gonzalez et al., 2003; Yang et al., 2004; Noertjojo et al., 2002; Cowie and Sharpe, 1998; Antony et al., 1995; Chan-Yeung et al., 2002). In the United States, extra pulmonary TB is associated with ethnic minorities and those born in other countries (Rieder et al., 1990) while in Asia origin, lymphatic TB occupies the front position of the risky infectious diseases (Cowie and Sharpe, 1997, 1998; Moudgil and Leitch, 1994; Nisar et al., 1991; Ormerod, et al., 1991). A study of Somali TB patients in Minnesota demonstrated frequent lymphatic TB (Kempainen et al., 2001).

1.2 Epidemiology of Tuberculosis in Yemen

Tuberculosis is still one of the major problems in Yemen. Yemen is considered as one of the high-burden countries in the region for a long time based on the evaluation of TB which has been conducted by National-Wide Survey of the Tuberculin Testing among children school (AL-Absi, 2007). TB is ranked 4th in the list of priority public health

problems. It is also estimated that TB is the 4th cause of death based on hospital statistics (TB guide, 2010). The annual expected incidence of new pulmonary TB smear-positive (NSS+) is 8480, and equal number of other forms of TB was estimated. The most recent estimates of TB in Yemen show that the annual incidence of new pulmonary TB smear-positive cases is 37 per 100,000 population, which means that, 7297 new pulmonary TB smear-positive cases per year would be expected in Yemen, and 8874 for other forms of TB cases; estimated 45 per 100,000 populations. Sana'a, the capital city of Yemen, occupied the first province with extra pulmonary TB cases and has the second highest number of cases of all forms of TB as compared to other provinces (AL-Absi, 2007). Table 1.1 below shows the trend of Case-Finding of tuberculosis in Yemen during 1995-2007

Table 1.2 illustrated the distribution of tuberculosis among Yemen governorates for the Year 2007. From the report, the city of Sana'a had the highest number of cases for pulmonary and extra pulmonary diseases compared to other governorates. The majority of tuberculosis patients in Yemen were between 15-54 years old, as shown in Figure 1.1. The report also showed that pulmonary tuberculosis is represented by 72% of the patients while the extra pulmonary tuberculosis represented 28%; most of them from Sana'a city (AL-Absi, 2007).

Table 1.1: All types of Tuberculosis in Yemen during 1995-2007(adapted from AL-Absi, 2007)

Years	New P.Sm+	Relapses	New P.Sm-	EP	Total
1995	3681	375	7390	3082	14528
1996	4371	298	7280	2415	14364
1997	4717	344	4251	2695	12007
1998	4896	297	4323	2867	12383
1999	5427	475	3824	3301	13027
2000	5565	440	4176	3470	13651
2001	4968	584	4383	3094	13029
2002	4259	436	4188	2794	11677
2003	3793	426	3435	2759	10413
2004	3434	377	3473	2732	10016
2005	3379	351	2780	2553	9063
2006	3337	311	2531	2559	8738
2007	3537	325	2196	2369	8427

Note: New P.Sm+ refers to new pulmonary TB smear-positive; New P.Sm- refers to new pulmonary TB smear-negative; EP refers to extra pulmonary TB.

Table 1.2: All types of Tuberculosis in Yemen Governorates for the Year 2007 (adapted from AL-Absi, 2007)

Governorates	New P.Sm+	Relapses	New P.Sm-	EP	Total
Abyan	123	15	89	38	265
Aden	287	39	133	172	731
Al-Baidha	68	4	35	33	93
Al-Dhalea	61	4	24	54	143
Al-Hodeida	704	58	165	244	1170
Al-Jawf	112	4	52	30	198
Al-Mahra	32	4	51	7	94
Al-Mahweet	41	6	47	38	132
Al-Mukalla	113	19	17	19	168
Amran	80	3	59	53	195
Dhamar	213	20	145	155	533
Hajjah	275	27	397	132	813
Ibb	194	10	21	111	336
Lahj	142	21	132	106	401
Mareb	50	2	37	38	127
Saadah	52	2	33	25	112
Sana'a city	313	39	261	570	1193
Sana'a Gov.	77	3	80	65	225
Sayioun	24	2	17	22	65
Shabwah	29	4	47	14	94
Taiz	508	38	241	433	1220
Raimah	39	1	14	18	72
Total	3537	325	2196	2369	8427

Note: New P.Sm+ refers to new pulmonary TB smear-positive; New P.Sm- refers to new pulmonary TB smear-negative; EP refers to extra pulmonary TB; Sana'a Gov. refer to Sana'a governorate.

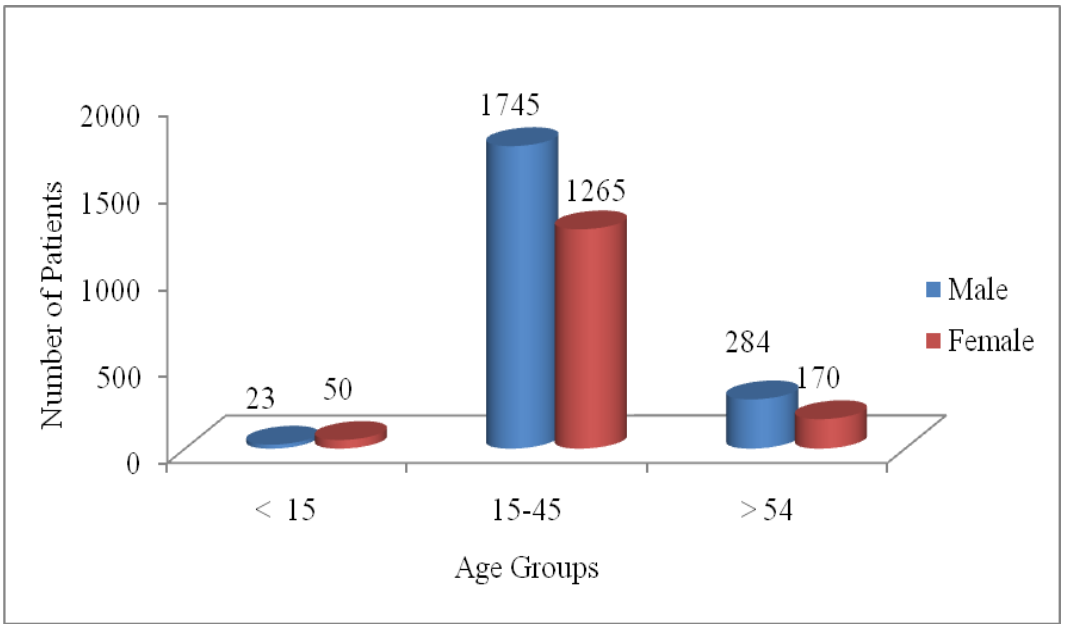

Figure 1.1 Age Distribution of Tuberculosis Patients in Yemen in the year 2007 (adapted from AL-Absi, 2007)

1.3 Transmission and Pathogenesis of Tuberculosis

As stated earlier, the bacterial disease, tuberculosis (TB) is transmitted when the patients who have pulmonary TB expelled the droplet nuclei through cough, sneeze, and even speak (Brewer and Heymann, 2004; Bjune, 2005; Gandy & Zumla, 2002). A droplet nucleus sized 10 μm can carry from 1 to 10 tubercle bacilli. On the other hand, tubercle bacilli particles get suspended in the air due to coughing or sneezing and are accordingly transported by the air currents which can carry them in the air for a long time and spread them all the way through rooms or buildings. Bacilli that are more likely to be inhaled are very often settled in the upper airways (American Thoracic Society 2000). It was reported that the most effective particles of droplet nucleus that can spread tuberculosis from person to another one are those sized 5 μm or less in diameter. Though small, they can still produce the anchorage in bronchioles and respiratory alveoli due to their ability

to avoid the mucus and ciliary's system action. Its small size helps them to remain suspended in the air for quite long periods of time. (Palomino et al., 2007; Friedman, 2001; WHO 1999).

Transmission of TB happens with high prevalence in crowded places with either none or bad ventilation (Hawker et al., 1999; Beggs et al., 2003; Elender et al., 1998 and Valin et al., 2005). A sputum smear-positive person having a pulmonary TB is four to six times more contagious than a smear-negative case (Menzies et al., 1999). On the other hand, sputum smear-negative culture-positive patients with pulmonary TB are still contagious to others too (Hernandez-Garduno, 2004; Behr et al., 1999). According to Jerant et al. (2000) and WHO (1999), environmental factors that best suit TB transmissions include the following:

1. Vulnerable individuals getting exposed to a contagious person in a relatively small, enclosed space,
2. Insufficient ventilation which may result in either poor dilution or in the removal of infectious droplet nuclei,
3. Air recirculation containing contagious droplet nuclei
4. Duration of disclosure, and
5. Susceptibility of the exposed person.

After inhalation, the droplet nucleus is passed down the bronchial tree, and implants in a respiratory bronchiole or alveolus. When inhaling tubercle bacillus, the tubercle creates an infection in the lung which relies on both the bacterial malignancy and the intrinsic microbicidal capability of the alveolar macrophage that ingests it. Bacteria can then

develop within the alveolar macrophage if they're capable to stay alive in its initial resistance.

The approximate dividing of tuberculosis bacteria, which grows slowly, happens every 25 to 32 hours within the macrophage (American Thoracic Society, 1999). Responses of two distinct T cell-mediated immune begin at 2-4 weeks. A reaction to a delayed-type hypersensitivity demolishes non activated macrophages including bacilli but leads to tissues necrosis and caseation.

Cell mediated immunity ends in microphages being activated into epithelioid cells with granulomas formation seen at the periphery of the caseation. A flexible organism, one that is able to multiple quickly external cells within cavities, survives inside macrophage and stops fusion between the lysosome and phagosome, and it also survive in relatively inactive state with only rare ruptures of division. Primary complex heals spontaneously in 1-2 months in 85-90% of cases and the tuberculin skin test becomes positive (Haslett, et al. 2002). Multiplication of *M. tuberculosis* is not enclosed in 10-15%, and that either local pressure effects, lymphatic extends to the pleura or pericardium, and ruptures into adjacent bronchus or pulmonary blood vessels happen due to lymph node enlargement.

In places where dissemination had arisen, the disease may develop fast to the evolution of miliary and meningeal tuberculosis. Furthermore, infection of foci can be set up in the bone, the lung, the genitourinary and gastrointestinal tracts, or lymph nodes, which may develop into a clinical disease. However, 85-90% of patients develop latent infection (positive tuberculin test or radiographic evidence of self-healed tuberculosis) 5-10% of

them reactivate during their life-time, resulting in post-primary disease. This is predominantly pulmonary (75%) and infectious (50% smear-positive).

Post-primary disease can result from the re-exposure to smear positive pulmonary tuberculosis and accordingly accounts for up to one-third of all cases. The possibility of infection after exposure is 30%, development of progressive primary disease is 30% and re-infection from other infectious cases is 50% and all these possibilities are increased in HIV of infected individuals. Further, where good immune function is retained in HIV, clinical disease resembles classical post-primary tuberculosis. However, where significant immunodeficiency has occurred, the presentation is more likely to be disseminated or extra pulmonary (Haslett, et al. 2002; Friedman 2001; and Mario et al. 2008).

1.4 Diagnosis of Tuberculosis

For proper and complete medical evaluation of TB diagnosis, the following steps have to be taken into consideration:

1.4.1 Determining the Medical History

One should obtain from the patient a complete history of the possible exposures to people with TB, Multidrug-Resistant TB (MDR-TB), past history of TB, previous positive tuberculin skin test, and previous history of treatment either for TB infection or any disease. An adequate clinical history should include information about household, immigration from high prevalence area, and about the medical factors which motivate factors for TB disease (e.g. diabetes mellitus, HIV infection, injection drug users and

homeless people) (American Thoracic Society/Centers for Disease Control and Prevention (2003), Correa (1997), Feja and Saiman (2005), Jacobs and Starke (1993), Taylor et al. (2005), Vallejo et al. (1994)).

1.4.2 Examining the Physical Symptoms

Physical examination is an essential part in evaluating, and obtaining the history of clinical signs and symptoms of pulmonary TB, which may include prolonged and productive coughs over two weeks duration, hoarseness, chest pain, or hemoptysis. Systemic symptoms of TB may involve unexplainable weight loss, fever, night sweats, appetite loss, easy fatigability, or chills.

1.4.3 Examining the Bacteriological Aspect

Such a step implies adopting the following examinations of:

1.4.3 (a) Sputum Smear

Bacteriological examination of sputum is referred to as acid fast bacilli (AFB). Such an examination is considered the only way in which the diagnosis of pulmonary tuberculosis can be confirmed. Whenever tuberculosis is suspected, three specimens of sputum should, at least, be collected and examined by microscopy and the examined samples will preferably be obtained within two days.

1.4.3 (b) Sputum Culture

Holtz et al. (2006) stated that the culture of tubercle bacilli is regarded as a confirmation step that is necessary for carrying out the sensitivity test which is in turn is essential for monitoring the initial and acquired drug resistance to anti-tuberculosis drugs.

1.4.4 Examining TB Radiographically

Chest x-ray screening has been used for active case finding for the last seventy years Golub et al. (2005), WHO (1994) and Friedman (2001), mentioned that the x-ray diagnosis of tuberculosis is unreliable because other chest diseases may resemble tuberculosis on x-ray, and because pulmonary TB may show many forms of radiographic abnormalities.

1.4.5 Tuberculin Skin Test (TST)

Tuberculin Skin Test is used to detect the *M. tuberculosis* infection in people who do not show symptoms of tuberculosis. Passalent et al. (2007) stated that the Mantoux test is a favored method for tuberculin skin test since the test depends on the *M. tuberculosis* infection produce hypersensitivity reaction to antigenic component of the organism. In order for an immune response to the test to be developed in a person, it generally takes 2-10 weeks after tuberculosis infection. Both false-positive and false-negative results occur. The reactions of false-positive tuberculin skin test occur in persons who were previously vaccinated against *M. tuberculosis* with BCG as well as those infected with non tuberculosis mycobacteria. On the other hand, reactions of false-negative tuberculin skin test may result from improper testing technique, concurrent infections, malnutrition, advanced age, immunological disorders, lymph reticular malignancies, corticosteroid therapy chronic renal failure, HIV infection and fulminant tuberculosis. When testing individuals with latent tuberculosis infection, they may have negative skin test reaction many years after infection.

1.5 Treatment of Tuberculosis

Two aims for treatment from tuberculosis; the first one prevents tuberculosis transmission by rendering the patients non-infectious and the second is to prevent morbidity and death by curing tuberculosis patients.

1.5.1 Treatment of Latent Tuberculosis Infection (LTBI)

The necessity lies in treating persons with latent tuberculosis infection which is actually to prevent and control the development of active disease in the future, also called as preventive therapy or chemoprophylaxis. Generally, those applying for treatment of latent TB are identified by the TST of persons in high-risk groups. In a period of six to nine months, isoniazid is administered (10 mg/kg/day or, at most, 300 mg/day) in every adult person vulnerable to develop an active disease (Robert, et al. 2002; Horsburgh, 2004; Castelo-Filho et al., 2004; Hopewell et al., 2006).

Such treatment reduces the risk of infection progress to active diseases, yet it does not keep the patient from exogenous exposure. The candidates for treating latent TB infection are those close to active pulmonary TB patients, persons who usually are in close contacts with active pulmonary TB patients (AFB smear-positive), persons with TST change (appositive test with >10 mm in period after a formerly negative test that has been applied earlier. In addition, for immunosuppressed persons (HIV) who have positive TST of > 5 mm, the treatment has been also applied. Other candidates are also those who are in close contact with immunosuppressed persons with a smear-positive TB patient. Moreover, persons with a chest X-ray image steady of residual TB, and without a history of previous anti-TB remedy are also close to active pulmonary.

Generally, medical doctors should confirm the absence of an active TB disease before starting the preventive chemotherapy with isoniazid. Initial steps can be taken by noticing the following: Chest X-ray is to be normal; and individual is to be asymptomatic and should exclude active TB, either pulmonary or extra pulmonary, particularly, in patients with moderate/severe immunodeficiency before beginning with the preventive chemotherapy. Furthermore, patient appropriate follow-up is necessary to make sure the supplement of a regular drug and at least 70% adherence to the preventive treatment regimen.

1.5.2 Treatment Regimens

Standard short course regimens are divided into an initial or bactericidal, phase and continuation or sterilization phase. Through the initial phase, the greater part of the tubercle bacilli are destroyed; symptoms resolve, and generally the patient become non-infectious. The continuation phase is necessary to remove persisting mycobacteria and avoid relapse (Toman, 2004; Palomino et al., 2007).

Isoniazid

Isoniazid is the most widely used anti-tuberculosis drug. It is given in doses of 5 mg per kg body weight per day up to maximum 300 mg per day. It can be safely used on pregnant women. A major side effect, hepatitis, develops in about 0.5 % of cases, if hepatitis is suspected or jaundice is observed, stop treatment (Rieder, 2004; WHO 2009).

Rifampicin

Rifampicin is a very potent, relatively non toxic drug. The daily dose for children and adults is 10 mg per kg body weight up to 600 mg per day. It can be safely used on pregnant women. When given in recommended dosages, rifampicin dose not cause any side effect with great frequency, particularly during continuous daily administration. One of the major side effects of rifampicin is hepatitis, although this is rare. Alcoholism, pre-existing liver diseases or the simultaneous administration of other hepatotoxic agents seem to increase the risk. The development of jaundice requires discontinuation of the drug (Rieder, 2004; WHO, 2009).

Pyrazinamide

Pyrazinamide is most active during the second and third month of therapy. The daily dose for adult is 25 mg per kg body weight and for children 20-40 mg per kg body weight up to maximum 2500 mg. It may be used safely on pregnant women. The most serious side effect of pyrazinamide is hepatitis. Joint pains and occasional attack of gout, due to the diminished excretion and accumulation of uric acid may occur less frequently (Rieder, 2004; WHO, 2009).

Isoniazid/Thioacetazone

Thioacetazone may help prevent the emergence of resistance to other drugs such as isoniazid, and therefore is administered in combination with isoniazid. The daily dose is 2.5 mg per kg body weight for adults and children up to maximum of 150 mg per day. Hepatitis is the major side effect that occurs as with isoniazid alone. Cutaneous reaction in patients treated with medication (due to thioacetazone) may be more serious than

other drugs. Exfoliative dermatitis or Stevens-Johnson syndrome may also occur and can be fatal.

Streptomycin

Streptomycin has strong effect on the elimination of tubercle bacilli in cavities of the lungs. The daily dose is 15 mg per kg body weight for adult 20 mg per kg body weight for children, up to maximum of one gram. The main toxic side effect of streptomycin is vestibular damage. The risk increases with the dose and age (Rieder, 2004; WHO, 2009).

Ethambutol

The primary use of ethambutol is to prevent emergency of resistance to the drugs. The daily dose in the first two months of chemotherapy is 25 mg per kg body weight in adults and 15 mg per kg body weight in children. When administered for more than two months, the dose should be reduced to 15 mg per kg body weight per day. Ethambutol may produce impairment of vision; a decrease in visual acuity, blurring and red-green color blindness (Rieder, 2004; WHO, 2009).

1.5.3 Regimens

1.5.3.1 Regimen for Positive Pulmonary

New cases of AFB smear positive pulmonary tuberculosis and other newly diagnosed patients who are seriously ill have severe forms of tuberculosis. The regimen include patients with tuberculosis meningitis, disseminated tuberculosis, tuberculosis pericarditis, peritonitis bilateral or extensive pleurisy, spinal disease with neurological complications, and smear negative pulmonary tuberculosis with extensive parenchymal involvement, intestinal or genito-urinary tuberculosis (Harries, 2004; WHO, 2009).

The regimen consists of initial (intensive) phase: 2HRZS(E); i.e., isoniazid, rifampicin, pyrazinamide and either streptomycin or ethambutol, given daily under strict direct observation for 2 months (8 weeks). When the patient has completed the initial phase of 2 months and the sputum smear is negative, the continuous phase is initiated. If the sputum smear is positive at two months, the initial phase of 4 drugs daily is continued for other four weeks under strict observation. After this, the continuation phase is initiated, regardless of sputum smear examination results (WHO, 2003).

Continuation phase: 6HT, e.g. isoniazid and thioacetazone daily for six months. For the patients who has serious adverse reactions (such as Stevens-Johnson syndrome, exfoliative dermatitis) ethambutol may be substituted with thioacetazone. Patients should come to the health facility every four week to collect their drugs for self administration at home (Table 1.3).

Table 1.3: Regimen for Positive Pulmonary (adapted from WHO, 2003)

Initial intensive phase					**Continuation phase**
Daily during month 1 and 2					Daily during months 3,4,5,6,7,and 8
	HR	Z	S or E		HT
Weight of patients (pre treatment weight	H+R combined tablet 100mg+150mg 150mg+300mg	Z tablet 500mg	S injection	E tablet 400 mg	H+RT combined tablet 100mg+50mg 300mg +150mg
less than 33kg	2 (100mg+150mg)	2	500 mg	2	2 (100mg+50mg)
33 kg to 50 kg	3 (100mg+150)	3	750 mg	2	3 (300mg+150mg)
51 kg or more	2 (150mg+300mg)	4	1 g	3	2 (300mg+150mg)

Note: H refers to isoniazid; R refers to rifampicin; Z refers to pyrazinamide; S refers to streptomycin; E refers to ethambutol; T refers to thioacetazone.

1.5.3.2 Regimen of Extra Pulmonary and Negative Pulmonary

Initial intensive phase: 2HTS (E), i.e., isoniazid, thioacetazone and either streptomycin or ethambutol, given daily for two months. Patients should come to the health facility every month to collect their drugs for self administration at home. Continuation phase: 10 HT i.e., isoniazid and thioacetazone daily for 10 months (Table 1.4). Patients should come to the health facility every month to collect their drugs for self administration at home (WHO, 2003).

Table 1.4: Regimen of Extra Pulmonary and Negative Pulmonary (adapted from WHO, 2003)

	Initial intensive phase		Continuation phase
	Daily during month 1 and 2		Daily during months 3- 8
	HT	S	HT
Weight of patients (pre treatment weight)	H 100g T 50 mg (combined tablet	S injection	H 100g T 50 mg (combined tablet
less than 10 kg	1/2	0.25 g	½
10 kg to 19 kg	1	0.5 g	1
20 kg 32	2	0.5 g	2
33 kg to 49 kg	3	0.75 g	3
50 kg or more	3	1.00g	3

Note: H refers to isoniazid; S refers to streptomycin; T refers to thioacetazone.

1.5.4 Re-Treatment of TB

The regimen according to WHO (1997) should be given to patients afflicted with tuberculosis diseases after completing the standard regimen (2 months of isoniazid, rifampicin, pyrizanamide and streptomycin or ethambutol then 6 months of isoniazid and thioacetazone). Re-treating TB involves passing through two phases:

Initial (Intensive Phase): this phase requires using 2HRZES/1HRZE, i.e. rifampicin, isoniazid, pyrazinamide and ethambutol, which is supplemented with streptomycin for the first two months (Table 1.5). Then, the same drug is used again, but this time without streptomycin. The dose should be taken daily for about one month and under strict, direct observation. When the patient completes the initial phase which consists of 2 months and when the sputum smear is negative, the continuous phase is started. If the sputum smear is positive throughout the three months, the initial phase of treatment with

four daily oral drugs lasts for another four weeks. If the patient is still smear- positive at the end of the fourth month, all drugs are stopped for 2-3 days, and a sputum specimen is sent to the laboratory for culture and for sensitivity testing. The patient should, then, start the continuation phase and refer to a specialist if possible.

Continuation Phase: the second phase demands using 5HRE, i.e., 5 months of isoniazid, rifampicin and ethambutol, which are given daily under direct strict observation. If the patient remains positive after the completion of the continuation phase, he is no longer eligible for this regimen. That is to say, this patient will be considered as a chronic case and will be dealt with accordingly.

Table 1.5: Regimen of Re-Treatment of TB (adapted from WHO, 2003)

Initial intensive phase					**Continuation phase**	
	Daily during month 1 and 2				Daily during months 3,4,5,6,7,and 8	
	S	HR	Z	E	HR	E
Weight of patients (pre treatment weight	S	combined tablet 100 mg+150 mg 150 mg +300 mg	tablet 500mg	tablet 400 mg	combined tablet 100 mg+ 50 mg 300 mg + 150 mg	400 mg
less than 33kg	500 mg	2 (100 mg+150 mg)	2	2	2 (100mg +150 mg)	2
33 kg to 50 kg	750 mg	3 (100 mg+150 mg)	3	2	3 (100mg + 150 mg)	2
51 kg or more	750 mg	2 (150 mg+300 mg)	4	3	2 (150 mg+ 300 mg)	3

Note: H refers to isoniazid; R refers to rifampicin; Z refers to pyrazinamide; S refers to streptomycin; E refers to ethambutol.

1.5.5 Treatment of Drug-Resistant Tuberculosis

Patients with drug resistance need careful supervision and management. Most resistance was to the effective drugs or at least to rifampicin and isoniazid, anti-TB drugs, or the so called multi-drug-resistant TB. Such a process consists of two phases as (WHO, 2010):

- Initial Phase: this phase involves taking the following for three months: streptomycin, kanamycin or amikacin, pyrazinamide, quinolones (ofloxacin or ciprofloxacin), ethambutol or cycloserine.– amikacin.

- Continuation Phase: in this phase three drugs should be used for 18-24 months, such asethionamide, quinolone, ethambutol or cycloserin.

1.5.6 Directly Observed Treatment (DOTS)

Direct observed treatment (DOTS) can improve adherence to treatment as it requires the worker to observe the patient when he is swallowing their medication. Around 10 million infectious patients have been successfully treated under the DOTS programme since it was first introduced on a global scale in 1995.

As reported by Sharma and Liu (2006), WHO describes the five fundamental principles of DOTS, as follows:

1. Political commitment and resources

2. Accurate diagnosis by AFB smear-positive

3. Standardized short-course treatment for all patients with directly observed

4. Regular provide with good and adequate free drug, and finally

5. Monitoring of the outcome of the patients.

In some parts of the world, a supply of 6 months of drugs for DOTS costs less than US$ 10 per patient. As ranked by the World Bank, the DOTS strategy is one of the "most cost-effective of all health interventions". Furthermore, an expected increase in drug resistance can be avoided by countries that employ DOTS such as cases in Cuba and Nepal in which levels of drug resistance showed a notable declination (WHO, 1994; WHO, 2002c). In 2004, 183 countries and territories implemented the DOTS strategy and that 83% of the world's population lived in DOTS-covered countries in the end of 2004. 4.4 million new cases were reported by DOTS programs and relapse TB cases in 2004; 2.1 millions were new AFB smear-positive. A total of 21.5 million TB patients, and 10.7 million AFB smear-positive patients were treated in DOTS programs over 10 years ranging from 1995-2004 (Palomino et al., 2007, Sharma and Liu, 2006, WHO, 2006a).

Throughout the world, case detection rate by DOTS increased from 11% in 1995 to approximately 45% by 2003, and exceeded 50% by the end of 2005. In 2003, DOTS treated around 1·8 million new smear-positive cases. This scale went on even in regions such as the WHO African region where multiple health crisis usually occurs as DOTS case detection rate rose from 24% to 50% during the years 1995 to 2003. DOTS cases where accounted the highest in India and China reaching 60% of the total increase of

cases in 2003. Furthermore, 20% of the global incidence of tuberculosis found in India which still has more cases than any other country.

In fact, the DOTS program showed a dramatic development during the year 1997 until early 2005, as it increased from 20 million (less than 2% of the population) to more than one billion people (90%) as stated by Revised National Tuberculosis Control Program (RNTCP). However, implementation of DOTS in China began in 13 of the 31 mainland provinces in 1991 and got coverage of 100% by the middle of 2005.(Dye et al., 2005; Frieden and Munsiff, 2005; Sharma and Liu, 2006; WHO, 2006a). However, such records were not similar in countries like Africa where the rates of TB continued to rise due to major failure of DOTS implementation which registered less than 75% cure rates while death rates were as high as 8% in patients co-infected with *M. tuberculosis* and HIV in 2002.

Weak health systems at times of HIV epidemic expansion is considered the major problem in Eastern Europe that showed continuing increases in TB occurrence rates throughout the 1990s, although the increase now appears to be pointed. This is still arguable in the sense that whether this statistic showed a failure of DOTS, or the result of the quick spread of the HIV epidemic. On the other hand, death rates in DOTS recipients remained stable at 5% in Central Asian countries which caused MDR-TB to consider the problem in both Eastern Europe and Central Asia (Dye et al., 2005; Frieden and Munsiff, 2005; Sharma and Liu, 2006; and WHO, 2006a).

In addition, and in disregards of substantial success with DOTS expansion, many countries will not probably meet the UN Millennium Development Goals' target of halving the prevalence of tuberculosis and the associated death rates between 1990 and 2015. Hence, more ground-breaking steps are to be taken as the public-health community moves beyond DOTS expansion to global tuberculosis control to better control TB globally (Sharma and Liu, 2006).

Yemen witnessed the first implementation of DOTS in 1995 by National Tuberculosis Program (NTCP) as a strategy of National TB control all over the country. Yemeni government worked to get the policy of the National TB control program (NTCP) in line with WHO TB control strategy of the Direct Observed Treatment, short course (DOTS). Patients were observed by nurses as they swallowed their medication in the first stage of the treatment. Once they missed their appointment, they were phoned to come or they were visited to their house by the nurses.

1.5.7 Adherence to TB Treatment

Consequences of non adherence to antituberculosis medications can be seen as a failure to treatment, continued transmission of the tuberculosis and drug resistance development. Thus, patients must be treated under directly observed therapy so as to ensure adherence and therapy completion (Cabrera et al., 2002 and Oza, 2002).

Furthermore, patients can be briefed and educated about TB diseases, methods of diagnosis, ways of transmission, treatment and prevention in order to improve the adherence to treatment (Cabrera et al., 2002).

1.6 Study Problem Statement

Tuberculosis is a major public health problem both in worldwide and Yemen. Tuberculosis disease forms significant portions of infectious disease and ranks second only to HIV/AIDS as a cause of infectious disease deaths (WHO 2004). No studies or even reports, on the cost of tuberculosis treatment and HRQoL have been conducted in Yemen. Yemen is considered as one of the high burden countries in the region for a long time based on the evaluation of TB which has been conducted by National-Wide Survey of the Tuberculin Testing among children school (AL-Absi, 2007, AL-Absi, 2010). Annual risk factor of TB infection in Yemen is 0.9% and prevalence 8.2 from total population (AL-Kamaly, 2006). Furthermore, tuberculosis patients face many problems related to physiological, psychological, financial and social problems. All of these problems have a great impact on their quality of life of TB patients (Dhingra and Rajpal, 2003).

1.7 Rational and Importance of Study

This quantitative study was planned and done to estimate the public health expenditures on tuberculosis treatments and to assess the HRQoL of pulmonary and extra pulmonary patients by interviewing the patients and health providers in medical centers in Sana'a, Yemen. This research seeks to invest its results by using an effective and accurate financial policy for the tuberculosis control. It may also help in the assessment of economic burden of tuberculosis in the capital city of Sana'a in several ways, such as allocation of resources and sets of priorities for tuberculosis control activities, giving estimation for the total budget needed for National Tuberculosis Control Programme and encouraging the health authorities to pay for prevention and early detection of