A NESTED CASE-CONTROL STUDY ON PREDICTORS OF TUBERCULOSIS RELAPSE, COMPLIANCE AND COST EVALUATION IN URBAN AREAS OF YEMEN

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BY

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LIST OF PUBLICATIONS AND PRESENTATIONS

M. S. Anaam, M. I. M. Ibrahim, A. W. Al Serouri, A. Bassili, A. Aldhubhani (2012). A nested case-control study on relapse predictors among tuberculosis patients treated in Yemen's NTCP. *Public Health Action Journal* 2(4); 168-173. http://dx.doi.org/10.5588/pha.12.0044.

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LIST OF ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ATS	American Thoracic Society
BCG	Bacille Calmette-Guerin
BMI	Body Mass Index
CAT	Category
CDC	Centers for Disease Control and Prevention
CDR	Case Detection Rate
CHWs	Community Health Care Workers
CIs	Confidence Intervals
CP	Continuous Phase
DOT	Direct Observed Treatment
DOTS	Direct Observed Therapy Short Course
DTC	District Tuberculosis Coordinator
GF	Global Facility
EMRO	Eastern Mediterranean Regional Office
GHWs	Government Health Care Workers
GLS	Governorate Laboratory Supervisor
GTC	Governorate Tuberculosis Coordinator
HC	Health Centre
HIV	Human Immunodeficiency Virus
IQR	Interquartile range

IP	Intensive Phase
IUD	Intravenous Drug Users
JATA	Japan Anti-Tuberculosis Association
JICA	Japan International Cooperative Agency
Kg	Kilogram
M	Median
M. tuberculosis	*Mycobacterium Tuberculosis*
MDR-TB	Multi-drug Resistant Tuberculosis
XDR-TB	Extreme-drug Resistant Tuberculosis
MLA	Medical Library Association
MoPH&P	Ministry of Public Health and Population
NTCP	National Tuberculosis Control Programme
NTI	National Tuberculosis Institute
OR	Odds Ratio
PHC	Primary Health Care
PTB	Pulmonary Tuberculosis
RIT	Research Institute of Tuberculosis
TB	Tuberculosis
USA	United State of America
IUATLD	International Union Against TB and Lung Disease
WHO	World Health Organization

KAJIAN KAWALAN KES BERSARANG KE ATAS FAKTOR PENENTU TUBERKULOSIS BERULANG, KOMPLIANS DAN PENILAIAN KOS DI KAWASAN BANDAR YEMEN

ABSTRAK

Tuberkulosis (TB) dianggap sebagai salah satu masalah kesihatan masyarakat yang paling utama di Yemen. Ia berada di tangga ke empat dalam senarai masalah utama kesihatan masyarakat. Penyakit TB berulang dan pesakit yang tidak komplians merupakan masalah yang serius yang membawa kepada pelbagai komplikasi. Kajian ini bertujuan untuk mengkaji pengaruh pelbagai jenis faktor ke atas penyakit TB berulang dan komplians pesakit serta menganggarkan bebanan dari segi ekonomi yang disebabkan oleh masalah ini. Kajian ini menggunakan reka bentuk kajian kawalan kes bersarang secara prospektif dan melibatkan seramai 814 pesakit TB pulmonari positif baru berdaftar bagi tempoh satu tahun (01-07-2007/31-06-2008) dalam 10 kawasan pentadbiran di Yemen. Pengumpulan data termasuk dua fasa utama: menemuramah pesakit yang terlibat pada tempoh akhir fasa intensif dan mengkaji semula kad perubatan dan pendaftaran TB mereka di akhir tempoh rawatan. Faktor-faktor yang diselidiki berkaitan masalah TB berulang adalah demografi, sosioekonomi, faktor berkaitan rawatan dan penyakit, dan juga faktor-faktor yang dinilai 2-3 bulan selepas rawatan, serta komplians terhadap terapi dengan ubat anti-TB. Manakala faktor yang dikaji ke atas masalah komplians adalah demografi dan sosioekonomi termasuk pengetahuan pesakit berkaitan penyakit TB, pendidikan kesihatan di pusat kesihatan dan kesan mudarat ubat anti-TB. Kajian ini juga menilai kos langsung daripada perspektif kerajaan. Ujian *Student T* dan *Mann-Whitney U* telah digunakan pada nilai alfa 0.05. Kaedah regresi logistik multivariat digunakan untuk menentukan faktor-faktor berkaitan kes TB berulang dan pesakit yang tidak

komplians. Analisis deskriptif menunjukkan 90% daripada responden dalam linkungan umur yang produktif (15-54 tahun). Terdapat 44 kes berulang dan 133 kes tidak komplians dalam kalangan sampel pesakit yang disusuli. Analisis regresi logistik multivariat menunjukkan status pekerjaan (*OR* 3.93, 95% *CI* 1.41, 10.99), bilangan batang rokok yang dihisap sehari (*OR* 11.76, 95% *CI* 1.55, 89.11), kehadiran rongga (*cavitations*) (*OR* 4.67, 95% *CI* 1.86, 11.70), kehilangan berat badan (*OR* 8.11, 95% *CI* 3.10, 21.39), kepatuhan pengambilan ubat dalam fasa rawatan TB berterusan (*OR* 17.94, 95% *CI* 1.69, 190.64), diabetes (*OR* 14.67, 95% *CI* 3.57, 60.20) dan komplians (*OR* 3.73, 95% *CI* 1.39, 9.99) merupakan faktor yang berkait secara signifikan dengan TB berulang. Manakala tahap literasi (*OR* 1.87, 95% *CI* 1.08,3.25), status pekerjaan (*OR* 2.19, 95% *CI* 1.26,3.80), masa perjalanan (*OR* 1.03, 95% *CI* 1.01,1.04), masa menunggu (*OR* 1.05, 95% *CI* 1.03,1.06), status tempat tinggal (*OR* 6.72, 95% *CI* 1.99,22.63), sokongan keluarga (*OR* 4.05, 95% *CI* 1.17,14.04), stigma (*OR* 1.75, 95% *CI* 1.06,2.89), tabiat mengunyah Qat (*OR* 3.26, 95% *CI* 1.89,5.60) dan pengetahuan pesakit tentang TB (*OR* 0.84, 95% *CI* 0.70,0.99) merupakan faktor risiko bagi masalah tidak komplians. Tempat tinggal juga merupakan faktor risiko bagi masalah tidak komplians dengan julat OR di antara 7.45, 95% *CI* 1.77, 31.42 (kawasan Metropolitan) dan 42.13, 95% *CI* 8.02, 221.37 (kawasan Hajjah) dalam kalangan kawasan pentadbiran. Dari segi kos perubatan langsung, terdapat perbezaan yang signifikan ($p < 0.001$) dalam kos median antara kumpulan berulang (*M*=93.00, *IQR*=91.86-93.42) dan tidak berulang (*M*=35.25, *IQR*=34.95-35.25). Kos yang ditanggung oleh kerajaan untuk merawat satu kes berulang dan tidak berulang adalah masing-masing US$92.31 dan U$$35.02. Kos tambahan yang ditanggung oleh kerajaan untuk merawat satu kes berulang adalah US$57.29. Walau bagaimanapun, dalam kalangan komponen perkhidmatan

kesihatan, perbelanjaan ubat menunjukkan kos yang tertinggi untuk pesakit tidak berulang dan berulang, masing-masing 59.0% dan 67.6%. Sebagai kesimpulan, dapatan kajian ini menunjukkan kadar tahap berulang (5.7%) dan tidak komplians (16.3%) adalah tinggi dalam kalangan pesakit TB. Terdapat ramai pesakit yang mempunyai pengetahuan yang terhad tentang penyebaran dan rawatan penyakit TB. Intervensi untuk mengurangkan masalah berulang dan kadar tidak komplians harus dilaksanakan. Kajian ini menyarankan penggunaan satu rawatan standard yang mengandungi rifampisin dalam fasa berterusan bagi rawatan TB berongga. Kajian ini turut menyarankan strategi untuk memperbaiki status sosioekonomi rakyat dan mencari rawatan TB yang berkesan kos.

A NESTED CASE-CONTROL STUDY ON PREDICTORS OF TUBERCULOSIS RELAPSE, COMPLIANCE AND COST EVALUATION IN URBAN AREAS OF YEMEN

ABSTRACT

Tuberculosis (TB) is considered to be one of the major public health problems in Yemen. It is estimated that TB is the fourth cause of death based on hospitals statistics. Relapse of TB and patients' non-compliance are serious problems leading to several complications. The present study was aimed to examine the influence of different factors on relapse of TB and patients' compliance as well as to estimate the economic burden as consequences of relapse. The study design was a nested case control study that included 814 new smear positive pulmonary TB patients registered during a one year period (01-07-2007/31-06-2008) in ten governorates of Yemen. Data collection included two main phases; interviewing the participants at the end of intensive phase and reviewing their medical cards and TB registers at the end of the treatment. Factors investigated on relapse were demographic, socioeconomic, treatment and disease-related factors as well as factors evaluated after 2-3 months of treatment, and compliance with anti-TB therapy, while the factors investigated on compliance were demographic and socioeconomic factors as well as patients' knowledge on TB, health education at health centre and adverse reactions of anti-TB drugs. A direct cost of relapse from government perspective was also evaluated. Student T-test and Mann-Whitney U test were used at alpha level of 0.05. Multiple logistic regression was employed to determine independently associated factors with relapse and patients' non-compliance. The descriptive analysis in this study showed that 90% of respondents were at their most economically productive age (15-54 years old). Forty four relapse and 133 non-compliant cases were identified during the

follow-up period. Multiple logistic regression analysis showed that the employment status (*OR* 3.93, 95% *CI* 1.41, 10.99), number of cigarettes smoked per day (*OR* 11.76, 95% *CI* 1.55, 89.11), presence of cavitations (*OR* 4.67, 95% *CI* 1.86, 11.70), weight loss (*OR* 8.11, 95% *CI* 3.10, 21.39), adherence in continuous phase (*OR* 17.94, 95% *CI* 1.69, 190.64), diabetes (*OR* 14.67, 95% *CI* 3.57, 60.20) and compliance (*OR* 3.73, 95% *CI* 1.39, 9.99) were significantly associated with TB relapse. While literacy (*OR* 1.87, 95% *CI* 1.08,3.25), employment status (*OR* 2.19, 95% *CI* 1.26,3.80), travelling time (*OR* 1.03, 95% *CI* 1.01,1.04), waiting time (*OR* 1.05, 95% *CI* 1.03,1.06), living status (*OR* 6.72, 95% *CI* 1.99,22.63), family support (*OR* 4.05, 95% *CI* 1.17,14.04), stigma (*OR* 1.75, 95% *CI* 1.06,2.89), Qat-chewing habit (*OR* 3.26, 95% *CI* 1.89,5.60) and patients' knowledge on TB (*OR* 0.84, 95% *CI* 0.70,0.99) were risk factors for non-compliance. The place of residence was also found to be a risk factor for non-compliance with a range of *OR* between 7.45, 95% *CI* 1.77, 31.42 (Metropolitan) and 42.13, 95% *CI* 8.02, 221.37 (Hajjah) among the governorates. In terms of direct medical cost, there was a significant difference in median cost between relapse (*M*=93.00, *IQR*=91.86-93.42) and non-relapse (*M*=35.25, *IQR*=34.95-35.25) groups; $p < 0.001$. The costs incurred by government to treat one relapse and non-relapse case were US$92.31 and U$$35.02, respectively. The extra cost incurred by government to treat one relapse case was US$57.29. However, the drug expenditures among health service components represented the highest cost for non-relapse and relapse patients (59.0% and 67.6%, respectively). In conclusion, the study findings showed high relapse (5.7%) and non-compliance (16.3%) rates among TB patients. A large proportion of patients had limited knowledge about the transmission and treatment of TB. Interventions to reduce relapse and non-compliance rates should be instituted. This study suggests using a

standard treatment regimen that contains rifampicin in the continuous phase for treatment cavitary TB. Strategies to improve socioeconomic status of the general population are recommended. It is also recommended that the cost effectiveness of TB treatment should be explored.

CHAPTER 1

INTRODUCTION

This chapter will provide an overview of tuberculosis in terms of pathogenesis and transmission, diagnosis, treatment and the current global strategy for control of the disease. Thereafter, a situation of tuberculosis, history development and organization, and organizational framework of National Tuberculosis Control Programme (NTCP) in Yemen will be explored. Then, an overview on relapse of tuberculosis as a problem in Yemen will be presented, followed by exploring the general themes of the economic impact of tuberculosis, research problem statement and rational of the study. Finally, the chapter will present the study aims and significance of the study.

1.1 Overview on Tuberculosis

1.1.1 Definition and Global Situation

Tuberculosis (TB) is a contagious disease caused by an organism called *Mycobacterium tuberculosis.* These organisms are also known as tubercle bacilli. Strikingly, about one third of the world's population is infected with *M. tuberculosis* and at risk of developing the disease. In the meantime, more than eight million people develop active tuberculosis every year. In 2009, 9.4 million cases of tuberculosis were reported globally which is equivalent to 137 cases per 100000 population. The mortality of this disease is high as two million people every year worldwide. Among all of tuberculosis mortality cases reported globally, 98% of the death incidences are reported from developing countries which represented 25% of all avoidable deaths. About 95% of global TB cases occurred in developing

countries, 75% of cases are in the most economically productive age group (15-54 years old). (World Health Organization [WHO], 2003a; WHO, 2003; WHO, 2010).

Although TB has the potential to cause the infection in various parts of the human body, it usually affects the lungs. The person can have TB infection itself which does not cause any symptom (TB disease) because the germs that cause TB disease can remain dormant or latent in the host's body for several years. People with TB infection whose immune system is weakened are more likely to develop a clinical TB disease. 5-10% of the people who have the TB infection may develop the disease at certain time of their lives. In the same context, leaving the individual who has the TB disease without treatment will infect an average of 10-15 people with TB every year. Without treatment, 50% of patients with pulmonary tuberculosis (PTB) will die within 5 years. However, 25% of patients will remain sick with chronic, infectious TB. Meanwhile, the other 25% will be spontaneously recovered and be healthy (due to strong immune defenses) but they could be sick again at any time. Remarkably, the co-infection diseases such as human immunodeficiency virus (HIV) will significantly increase the risk of developing TB. For instance, 50% of the people infected with both HIV, and *M. tuberculosis* will become sick of TB during their lifetime (Corbett *et al.*, 2003; WHO, 2003a; WHO, 2004).

1.1.2 Tuberculosis Pathogenesis and Transmission

The most important source of infection is a person with smear positive PTB. Untreated active smear positive PTB case will infect an average of 10-15 people per year (WHO, 2003a). The tubercle bacilli can not survive when they are exposed to the direct sunlight for more than 5 minutes, but they can survive in the dark for long periods (WHO, 2004). It implies that the transmission of TB usually occurs indoors.

The extent of exposure to the droplet nuclei (duration and dose) and the susceptibility of the host determine an individual's risk of infection (Rieder, 1999).

Primary infection occurs when a person is newly exposed to tubercle bacilli. Droplet nuclei are tiny enough to escape the mucocilliary defense of the bronchi, lodge in the terminal alveoli of the lungs and begin to multiply forming a lesion called Ghon focus. The Ghon focus and related hilar lymphadenopathy form a primary complex. Usually the immune response controls multiplying bacilli, resulting in a latent infection with a few dormant bacilli. In such cases, the only evidence of infection may be a positive tuberculin skin test. In 5% of the cases, the bacilli overwhelm the immune response and multiply resulting in a primary TB within a few months to a maximum of 5 years (Enarson *et al.*, 2000). Post-primary TB occurs when the latent infection is reactivated or when the individual is reinfected (van Rie *et al.*, 1999; Sonnenberg *et al.*, 2001; Lillebaek *et al.*, 2002). Post-primary TB is characterized by extensive tissue destruction and cavitation, and mainly affects the lungs but can also involve the other organs (WHO, 2004).

1.1.3 Tuberculosis Diagnosis

There are two approaches to TB diagnosis; the first approach is to diagnose TB infection, while the second one is to diagnose TB disease. The highest priority for TB control is to detect and cure the TB disease especially infectious cases, patients with sputum smear positive PTB, because these patients are the main sources of TB transmission (WHO, 2003).

1.1.3 (a) Diagnosis for Tuberculosis Infection

Persons with TB infection refer to those who have been exposed to someone who has TB disease and have been infected with *M. tuberculosis*. However, they may not feel sick or have symptoms and can not spread the TB to the others. The Mantoux tuberculin skin test is the standard method for identifying the TB infection. Reaction to a tuberculin skin test is measured 48 to 72 hours after the injection and classified as positive when ≥ 5 mm diameter in the absence of previous Bacille Calmette-Guerin (BCG) vaccination and ≥ 10 mm diameter in those who have been vaccinated with BCG (American Thoracic Society [ATS], 2000; Ayatollahi, 2006).

The tuberculin skin test is a valuable tool, but it is not perfect. Several factors can affect skin test reactions. For example, a false positive test result may present when persons have an infection with mycobacteria other than *M. tuberculosis* or have had vaccination with BCG. Conversely, a false negative skin test may occur in persons who have anergy, HIV infection, severe malnutrition, recent TB infection, or immunosuppressive therapy (ATS, 2000; Centers for Disease Control and Prevention [CDC], 2009). In countries where TB is prevalent, the TB skin test is of little value in the diagnosis of TB in adults. A positive tuberculin skin test does not by itself distinguish *M. tuberculosis* infection from TB disease (ATS, 2000; CDC, 2005).

1.1.3 (b) Diagnosis for Tuberculosis Disease

Diagnosis for Pulmonary Tuberculosis. Diagnosis of pulmonary TB can be performed by sputum smear microscopy alone or in combination with a sputum culture, and chest radiography if resources are available. Direct microscopic examination of the sputum is the most cost-effective method of detecting the infectious cases in high prevalence countries, because it is inexpensive, rapid, and

easy to perform (WHO, 2004; Ozkutuk *et al.*, 2007). Microscopic examination by acid fast staining procedures such as Ziehl-Neelsen method is the first step to detect acid fast bacilli (AFB). Although sensitivity of direct microscopic examination ranges from 22 to 78% when compared to sputum culture as a gold standard, obtaining multiple samples can increase the sensitivity of sputum microscopy (Aung *et al.*, 2001; Yassin and Cuevas, 2003). Tuberculosis suspects defined as persons who cough for more than two weeks should submit three sputum samples for microscopy (WHO, 2003b). The chances of finding tubercle bacilli are greater with three samples than two or one sample. In most cases, a chest X-ray is unnecessary; except for individuals for whom there is clinical suspicion of TB despite negative sputum smear (Kisa *et al.*, 2002; WHO, 2003b; WHO, 2004; Ozkutuk *et al.*, 2007). In some countries, the initial diagnosis test is a chest X-ray (Jaramillo, 1998). However, sputum smear microscopy must always be performed for better diagnosis. Although culture is much more sensitive than microscopy, routine sputum culture for diagnosis is not feasible and thus, not recommended especially in poor countries (Srikanth *et al.*, 2009). Sputum culture results take a long processing time which may be too late to monitor the progress of the diagnosis and treatment.

Diagnosis for Extra-pulmonary Tuberculosis. Definitive diagnosis of extra-pulmonary TB is often difficult. Diagnosis may be presumptive, provided you can exclude other conditions. The diagnosis of individual cases of extra-pulmonary TB is a clinical activity. The degree of certainty of diagnosis depends on the clinical history, the availability of diagnosis tools such as specialized X-rays or biopsy procedures (WHO, 2004). Many patients with extra-pulmonary TB also have co-existent pulmonary TB, therefore they need sputum examination for AFBs.

1.1.4 Disease Classification

Tuberculosis disease is classified by site of the disease as pulmonary and extra-pulmonary TB. Definitions of disease classification are described as follows:

Pulmonary Tuberculosis. Pulmonary TB refers to disease involving the lung parenchyma. A patient with both pulmonary and extra-pulmonary TB should be classified as a case of pulmonary TB. There are six categories of pulmonary TB at admission to TB care: 1) New, defined as a patient who has never had treatment for TB or who has taken anti-TB drugs for less than one month. New patients are sub-grouped into new smear positive and new smear negative; 2) Relapse, defined as a patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) TB again; 3) Treatment after failure, defined as a patient who has started on a re-treatment regimen after having failed previous treatment; 4) Treatment after default, defined as a patient who returns to treatment, positive bacteriologically, following interruption of treatment for 2 months or more; 5) Transfer in, defined as a patient who has been transferred from another TB register to continue treatment; and 6) Other, defined as all cases that do not fit the above definitions. This group includes chronic case, a patient who is sputum positive at the end of a re-treatment regimen (treatment after relapse, treatment after failure and treatment after default), (WHO, 2003c).

Extra-pulmonary Tuberculosis. Extra-pulmonary TB refers to TB of organs other than the lungs such as pleura, lymph nodes, bones, abdomen, skin, joints, genitourinary tract and meninges (WHO, 2003b).

1.1.5 Tuberculosis Treatment

Treatment of TB based on standardized short course chemotherapy regimens is the cornerstone of disease control. Standardized regimens have advantages over individualized regimens because they reduce errors in prescription, facilitate estimates of drug needs and facilitate staff training. There are three main properties of anti-tuberculosis drugs: bactericidal activity, sterilizing activity and the ability to prevent resistance. Isoniazed (H) and rifampicin (R) have a powerful bactericidal effect; in addition to this effect rifampicin is considered the most potent sterilizing drug available. Pyrazinamide (Z) and streptomycin(S) are also bactericidal drugs. Ethambutol (E) and thiocetazone (T) are bacteriostatic drugs and used to prevent the emergence of resistant bacilli (WHO, 2004). According to the World Health Organization guideline in tuberculosis treatment (WHO, 2004), the treatment period consists of two phases: an initial phase and a continuation phase, and there are four categories (CAT) for TB treatment:

Category I (CAT I). This category is used for tuberculosis patients who are: new smear positive patients, new smear negative PTB with severe disease and severe forms of extra-pulmonary tuberculosis. The total duration takes at least eight months; an initial phase is two months with isoniazed, rifampicin, pyrazinamide and ethambutol followed by the continuation phase for six months with isoniazed and ethambutol (2RHZE/6HE).

Category II (CAT II). This category is used for patients with treatment after relapse, treatment after failure and treatment after default. The total duration takes at least eight months; three months for an initial phase and five months for a continuation phase. Treatment for an initial phase consists of: 1) two months with isoniazed, rifampicin, pyrazinamide, ethambutol and streptomycin and 2) one month

with isoniazed, rifampicin, pyrazinamide and ethambutol. Treatment for the continuation phase takes at least five months with isoniazed, rifampicin and ethambutol (2RHZES/1RHZE/5RHE).

Category III (CAT III). This category is used for patients with new smear negative pulmonary (other than CAT I) and less severe forms of extra-pulmonary tuberculosis. CAT III takes also at least eight months (2RHZ/6HE). It is similar to CAT I but ethambutol may be omitted during the initial phase for patient whose a chest X-ray shows non-cavitary; smear negative PTB patients who are known to be HIV-negative. According to WHO recommendation, recently the use of this treatment regimen has been stopped in NTCP of Yemen. The cases under this category were included into the category one.

Category IV (CAT IV). This category is used for patients with chronic and multidrug resistant tuberculosis (MDR-TB) cases, defined as patients with resistance to at least both isoniazid and rifampicin. This category uses individualized regimens depending on the drug sensitivity test.

At the end of the treatment course, each patient is evaluated and assigned into one of the six categories of treatment results: 1) cured, defined as a patient who is sputum smear negative in the last month of treatment and on at least one previous occasion; 2) completed, defined as a patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure; 3) failed, defined as a patient who is sputum smear positive at five months or later during treatment; 4) died, defined as a patient who dies for any reason during the course of treatment; 5) defaulted, defined as a patient whose treatment was interrupted for two consecutive months or more; and 6) transferred out, defined as a patient who has been transferred

to another recording and reporting unit and for whom the treatment outcome is not known (WHO, 2003c).

1.1.6 Disease Control

The most cost-effective public health measure for the control of tuberculosis is to detect and cure infectious tuberculosis patients, defined as patients with smear positive PTB (WHO, 2003b). However, tuberculosis control programmes also provide the same care for other types of TB patients as well.

Tuberculosis has been recognized as a global emergency because of the increasing number of patients worldwide. Tuberculosis as an emergency was declared by WHO since 1993 (WHO, 1998; Gandy and Zumla, 2002). To face this emergency, the WHO has developed a new policy and strategy. The current global strategy for effective control is the direct observed therapy short course (DOTS). It has five key components. First, is the government commitment to sustain TB control activities. Second, is the case detection by sputum smear microscopy among symptomatic patients. Third, is the standardized treatment regimen of at least six to eight months for confirmed sputum smear positive cases, with direct observed therapy (DOT) for at least the initial two months. DOT means that an observer watches the patient swallowing their tablets in a way that is sensitive and supportive to the patients' needs. This ensures that a tuberculosis patient takes the right anti-tuberculosis drugs in the right doses at the right intervals. In theory, the observer may be a health worker or a trained community member. However, in practice, the observers are usually family members of the patients. Fourth, is a regular, uninterrupted supply of all essential anti-tuberculosis drugs. Fifth, is a standardized recording and reporting system that allows assessment of treatment results for each

patient and overall of the tuberculosis control programme (WHO, 2003a). The DOTS strategy has been implemented worldwide with a wide variation in success of the programme.

1.2 Tuberculosis Situation in Yemen

Yemen is one of the intermediate TB burdened countries in the Eastern Mediterranean Region. Tuberculosis is one of the major public health problems in Yemen ranking 4th in the list of priority public health problems (NTCP, 2010).

1.2.1 Demographic and Epidemiological Data

Yemen is an Arabian country located in the south west of Arabian Peninsula with 24 million population. It is located in an area of 555000 km^2. Yemen is divided into 21 governorates which subsequently divided into 333 districts. Table 1.1 shows the demographic and the epidemiologic data of Yemen.

Table 1.1: Demographic and Epidemiological Data (2011)

Demographic data						
Birth rate (per/1000 population)			32.6			
Death rate (per/1000 population)			6.8			
Infant mortality rate (per1000 live birth)			53.5			
Life expectancy at birth male			62.1			
Life expectancy at birth female			66.3			
Economy						
GNI per capita US$			2300			
Education						
Rate of primary school enrolment			72.6%			
Rate of illiteracy			36.1%			
Proportion of population in broad age group						
Age	0-14		15-64		65+	
%	43.0		54.4		2.6	
BCG coverage						
Year	2006	2007	2008	2009	2010	2011
Coverage	67%	64%	60%	58%	65%	59%
Epidemiology of TB 2009						
Total population	24 million					
Annual Incidence of PTB smear positive	6,000 (25/100000 population)					
Total Incidence of all forms of TB	14,400 (60/100000 population)					
Prevalence	18,720 (78/100000 population)					
Mortality	(2000-2500) person (9.4/100000 population)					

Source: https://www.cia.gov/library/publications/the-world-factbook/geos/ym.html

Based on hospitals statistics it is estimated that TB is the 4th cause of death in Yemen. As shown in the previous table, there are about 2000-2500 TB cases of all forms that die from TB annually with mortality rate of 9.4 per 100000 population.

According to the Yemen NTCP guideline, the latest estimated incidence of all forms of new TB cases was 14400 with a rate of 60 per 100000 population. The estimated incidence rate of new smear positive PTB was 25 per 100000 population with an estimated 6000 new smear positive cases in 2009.

During 2009, a total of 3576 new smear positive PTB cases were reported to NTCP with notification rate of 15 per 100000 population. The case detection rate (CDR) was 60%. All forms of notified TB cases were 8248 TB cases. The CDR was

57%. The estimated prevalence of all forms of TB cases is 78 per 100000 population with 18720 estimated prevalent cases. There were 1900 TB deaths in 2009, with a mortality rate of 7.9 per 100000. Seventy three percent (73%) of all notified new pulmonary smear positive cases are in the most productive age groups (15-49 years old). The male/female ratio reached up to 1.3 in 2009 (NTCP, 2010).

DOTS coverage reached 100% within Ministry of Health facilities in 2007. Treatment success rate increased from 50% before DOTS implementation to 84% for 2008.

Tuberculosis case notification declined steadily from 2000. However, the question of whether this decrease was true epidemiologically or related to operational factors is still unsolved. However, the last survey conducted in 2009, showed that the incidence of new smear positive PTB was 25 per 100000 population (NTCP, 2010).

Tuberculosis case detection among children was always below 2 per 100000 population indicating that TB among the children was under detected. This is because children at younger ages can not produce sputum and diagnosis by primary health care remains difficult (NTCP, 2010).

According to the multidrug resistant survey done by the Research Institute of Tuberculosis (RIT) Japan during the year 2004-2005, MDR was found to be 2.9% among new smear positive cases and 11.3% among previously treated cases.

Based on a recent survey completed on TB-HIV co-infection in collaboration with the HIV-AIDS programme, it has been observed that among 900 TB cases there were 6 HIV positive cases which was below < 1% (NTCP, 2010; WHO, 2010).

1.2.2 History Development and Organization of NTCP

Tuberculosis control programmes were launched in 1970s in previous two parts of Yemen (North and South). After the unification on the 22nd May 1990, the Ministry of Public Health and Population (MoPH&P) established the directorate of NTCP within the General Directorate of Public Health.

In 1983, the cooperation between Yemen and Japan International Cooperative Agency (JICA) was started. The WHO and the JICA are the only Donor Agencies for Yemen NTCP. In 2001, MoPH&P assigned a running budget for NTCP compared of sponsoring only the NTCP staff salaries in the past. Along with MoPH&P and WHO, the Global Facility (GF) also contributed supporting the NTCP in 2004.

NTCP is a tool for TB control strategy implementation within a national health system. As such, the NTCP is a vehicle for the DOTS strategy. NTCP policies, plans and activities are designed to achieve efficient case finding and treatment of TB patients. The NTCP should be countrywide, continuous, permanent and integrated into the existing national health services. For patients, the NTCP aims to cure the disease, quickly restore their capacity for daily life activities and allow them to remain within their family and community (NTCP, 2010). For the community, the purpose of the NTCP is to stop the spread of TB infection and prevent a costly public health crisis.

1.2.3 NTCP Organizational Framework

The Ministry of Public Health and Population established a National Tuberculosis Control Programme in 1995. It is a detailed plan of action for effective TB control. There must be four levels of responsibility to ensure efficacy of TB

control: peripheral, district, governorate and central levels. Each of these levels is well defined with different tasks (NTCP, 2010).

Peripheral level. The NTCP is implemented through the network of health centers and health units at the peripheral level and the role of these facilities is to offer basic TB services to the patients such as DOT, health education, defaulters tracing, identifying TB suspects and refer them to TB diagnostic centres. A medical officer or medical assistant in-charge of the peripheral health facilities is responsible for the implementation.

District level. It is the basic unit of management for DOTS implementation serving a population of 30000-150000. The Director General and Primary Health Care Director of Governorate Health Office designate, in consultation with Governorate TB Coordinator (GTC), a District TB Coordinator (DTC), who is responsible of all TB control activities within the district (diagnosis, treatment, follow up, training, supervision, logistics, etc.).

Governorate level. The Director General of Health Office gives guidance and support to the Primary Health Care Director in implementing the NTCP policies throughout the network of Primary Health Care (PHC) in the Governorate. The Director General of Health Office appoints a GTC who is responsible of planning and supervision all TB control activities within the Governorate. The Director General of Health Office also appoints the Governorate Laboratory Supervisor (GLS) who is responsible for quality control of TB laboratories in the Governorate.

Central level. The primary responsibility is to ensure that TB control is implemented effectively and uniformly throughout the country. The Directorate of Tuberculosis Control in MoPH&P is the central unit of National Tuberculosis

Control Programme under guidance and instructions of Director General of Diseases Control and Surveillance and Under-Secretary of Primary Health Care.

1.2.4 Relapse of Tuberculosis in Yemen

Relapse of tuberculosis is defined as the circumstance in which a patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) TB (WHO, 2003a).

Relapse of tuberculosis is a serious problem that could hamper TB control and the success of the National Tuberculosis Control Programme in Yemen. The relative relapse rate is high among all years exceeding the acceptable norm (< 5%) (Caminero *et al*., 1996; WHO, 1997; Connolly *et al*., 1999; Vernon, *et al*., 1999; Chang *et al*., 2006). Table 1.2 shows the number of new positive TB cases and relapse cases as well as the relative relapse rate during the past years (1995-2009).

Table 1.2: New Smear Positive and Relapse Cases during 1995-2009

Year	New Smear Positive Cases	Relapsed Cases	Relative Relapse Rate (%)
1995	3681	375	9
1996	4371	298	6
1997	4717	344	7
1998	4896	297	6
1999	5427	475	8
2000	5565	440	7
2001	4968	584	11
2002	4259	436	9
2003	3793	426	10
2004	3434	377	10
2005	3379	351	9
2006	3337	311	9
2007	3537	325	8
2008	3540	411	10
2009	3576	314	8
Average	**4165**	**384**	**8.4**

Source: NTCP Report 2010

Referring to the Table 1.2, it was noticed that after simultaneous decline of TB till 2006, new cases were seen to increase again from 2007. Regardless of this negative point of TB control in Yemen, the country is still among the moderate TB prevalence countries in the world. Hence, the resurgence of tuberculosis is not a case, as far as the threat of relapse, especially if such increase can be justified. The relapse of tuberculosis is an important issue and has to be taken into consideration. The relapse rate exceeded the acceptable norm (i.e., < 5%) and could seriously affect the success of DOTS strategy applied in the country.

Understanding the phenomenon of the relapse of tuberculosis is important to identify the factors that actually contribute to the phenomenon. Hence, a list of factors were explored which include:- demographic, socioeconomic, co-morbidity, treatment and disease-related factors as well as patients' compliance and the factors evaluated after 2-3 months of treatment (i.e., presence of positive smear at the end of the second or the third month and gaining weight at the end of the second month).

1.3 Patients' Compliance to Anti-Tuberculosis Treatment

Compliance means following a rule or procedure as directed. For example, for a TB patient compliance means taking anti-TB drugs as scheduled (WHO, 2003a).

Non-compliance with the treatment of tuberculosis is a major problem that leads to treatment failure, relapses and emergence of drug resistance (Comolet *et al*., 1998; Al-Hajjaj and Al-Khatim, 2000; Pandit and Choudhary, 2006; Bagchi *et al*., 2010; Vijay *et al*., 2010). Non-compliance places the patients at risk for the individual health, their family and the wider community, as well as wasting health resources (McLean, 2003).

The public health priority of a National Tuberculosis Control Programme is the cure of smear positive tuberculosis cases, while preventing the emergence of drug resistance. Patients' compliance as a key factor in treatment success should be ensured to achieve this priority (WHO, 2003).

Many studies have consistently found that non-compliance to anti-TB treatment was associated with relapse of tuberculosis (Selassie and Wilson, 2002; Thomas *et al*., 2005; Selassie *et al*., 2005; Picon *et al*., 2007). According to NTCP annual report of 2006, a default rate was high (0-20%) in all Yemeni governorates exceeding the WHO norm (10%).

Compliance is a critical factor in successful TB control; hence it becomes a priority in this study. The patients' compliance was studied as an independent variable of relapse and a dependent. A list of the independent variables expected to affect the patients' compliance were explored. The factors studied on compliance were demographic, socioeconomic and knowledge on TB and its treatment as well as education at the health centre and presence of adverse reactions.

1.4 Economic Impact of Tuberculosis

Tuberculosis is the first killer disease that kills nearly two million people every year at their most economically productive age (15-54 years old). On average, a TB patient loses three to four months of work time due to illness, equivalent to 20-30% of annual household income and about 15 years of income lost due to premature death (WHO, 2003). In addition to the devastating economic costs, TB imposes indirect negative consequences among women with TB who are unable to practice their essential responsibilities for their families; the person with TB can be rejected from community, friends and even family. Increasing loss of income in seeking health care for TB makes the households changing their strategies to reduce total family expenses. Thus, the children could miss their education opportunities, food intake could decrease and the family might need to sell some of their assets and borrowing money from others (WHO, 2000; Elamin *et al.,* 2008).

1.5 Problem Statement

Yemen as in many developing countries is trying to eliminate this killer disease. According to WHO global tuberculosis database 2007 and some data from the statistics department in National Tuberculosis Control Programme, Yemen is close to WHO target of treatment success rate (85%). Despite of this high success rate, the relapse of tuberculosis remains a problem in TB control of Yemen where the relative relapse rate ranged between 6 to 11% during all previous years i.e., from 1995 to 2009 (Table 1.2).

Based on 2006 report by NTCP, it is estimated that the relative relapse rate was between 3% to 20% in all governorates as a whole and between 0% to 29%

among urban areas (Table 1.3). The high rate of relapse could be the leading cause for transmission of resistant *M. tuberculosis*.

Table 1.3: Relative Relapse Rate in Yemen (2006)

Region	2006	Overall Country			Urban Areas		
	Governorate	**NSm+**	**Relapsed**	**RR (%)**	**NSm+**	**Relapsed**	**RR (%)**
South	**Abyan**	162	12	7	98	3	3
	Aden	239	46	16	239	41	14
	Lahj	149	6	4	96	2	2
	Taiz	478	40	8	308	34	10
Middle	**Al-Baidah**	57	14	20	47	2	4
	Al-dhale	69	5	7	52	4	7
	Dhamar	208	14	6	71	7	9
	Ibb	142	13	8	113	9	7
West	**Al-Hodeidah**	689	57	8	194	26	12
	Al-Mahweit	62	2	3	8	0	0
	Hajjah	256	35	12	27	11	29
	Raimah	36	1	3	13	0	0
North	**Al-Jawf**	46	5	10	7	0	0
	Amran	63	6	9	18	2	10
	Metropolitan	315	25	7	66	8	11
	Saddah	62	2	3	16	0	0
	Sana'a	75	3	4	16	0	0
East	**Al-Mahara**	17	1	6	15	1	6
	Hadramout	120	19	14	69	7	9
	Mareb	57	3	5	28	3	10
	Shabwah	35	2	5	16	0	0
	Total	**3337**	**311**	**8.5**	**1517**	**160**	**9.5**

NSm+ =New Smear Positive Cases; RR= Relative Relapse Rate; Source: NTCP Report 2006

Relapse of tuberculosis results in a great negative impact on tuberculosis care for patients, the TB control programme and the local community. For the patient, relapse of tuberculosis can lead to lose patients' trust on the NTCP, the use of more complex and longer treatment regimen, increased possibilities of unsuccessful treatment outcomes, higher chances to develop drug resistance, and higher risks of morbidity and mortality are main concerns (WHO, 2006). For the TB control programme, the defaulters of relapsed cases remain infectious and could be the leading cause for transmission of resistant *M. tuberculosis* to the other people in the

community (WHO, 2006). In addition, larger amounts of resources (e.g., financial and human resources) needed to be allocated to treat recurrent patients. If there is high number of relapsed cases, it will be difficult for any programme to control the tuberculosis. Therefore, relapse has serious implications on both individuals and communities.

1.6 Rational and Importance of the Study

Yemen is one of the developing countries where tuberculosis is a major concern. Tuberculosis costs the country wasting a lot of resources and relapse of TB complicates this situation. To study the factors which may be associated with relapse is a promising tool to reduce the incidence of TB relapse and preventing resurgence of MDR tuberculosis. Once the relapse incidence is reduced the resources consumed to control TB will be reduced. Hence, there will be less burden economically on the government, society or individual. Money saved can be then used for TB control.

Relapse of TB is defined as the circumstance in which a patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) TB (WHO, 2003a). A recurrent episode can be caused by either endogenous relapse (reactivation) of the same strain of the initial episode, following insufficient bacterial cure, or exogenous new infection of a strain of *M. tuberculosis* (reinfection). TB recurrence has been reported to occur within an acceptable rate (< 5%) after a wide application of effective anti-TB drugs in combination for at least 6 months in a largely HIV-negative environment (Weis *et al.*, 1994; Chan *et al.*, 1994). However, recent reports and studies showed that there was a noticeably increasing trend in TB recurrence globally (Connolly *et al.*, 1999; Sonnenberg *et al.*, 2001; Panjabi *et al.*, 2007; Glynn *et al.*, 2010; Nyamogoba *et al.*, 2012). In 2009, more than 270,000 recurrent cases were reported

worldwide (WHO, 2010). Evidence from recent studies suggests that the TB recurrence rate has surpassed that of TB incidence (Connolly *et al*., 1999; Verver *et al*., 2005). Being an important index to assess the long-term effectiveness of TB control programme, the increased recurrence rates have raised significant concerns among researchers and public health practitioners on the current TB control strategy, i.e., "Directly Observed Therapy, Short-course". Moreover, heavy burdens imposed by elevated recurrence risk on both individual patients and TB Control Programmes call for intensive investigations and practical interventional strategies to control this trend.

Relapse of tuberculosis is a serious problem that could hamper TB control and success of National Tuberculosis Control Programme in Yemen and found to be higher than the acceptable norm (< 5%). Through the investigation of TB relapse rates and its associated risk factors, the burden from TB relapse would be quantified and important messages regarding the control of TB relapse will be conveyed to both National TB Control Programme and other programmes under similar settings.

During the last 5 years a high cure rate (85%) was achieved in Yemeni DOTS programme. In contrast, the unduly relative relapse rate (3% to 20%) has been seen. It is generally accepted that if DOTS is widely practiced to a high standard and with a high cure rate, the tuberculosis epidemic should subside. High cure rates with rifampicin-based chemotherapy throughout the treatment should also be associated with a low relapse rate (< 5%). Some reports suggested that in a routine setting relapse rates can be considerably higher, for various reasons such as use of ethambutol in the continuation phase instead of rifampicin or a high TB transmission pressure in the community (Chan *et al.*, 1994). If this is true, then even after having achieved the global goal of 70% case detection rate and 85% cure rate, the

elimination of the TB problem will not be guaranteed. Therefore, it is necessary to address the possibility of unduly high relapse rates in Yemen under apparently high cure rates in routine programme conditions.

1.7 Main Aims of the Study

The general aims of this study are to reduce relapse rate of tuberculosis, enhancing patients' compliance and to determine the economic burden of tuberculosis relapse in Yemen. To achieve these aims, the following specific objectives were investigated:

1. To study, under DOTS programme conditions, the effect of different factors on TB relapse in NTCP of Yemen.
2. To study the effect of different factors on patients' compliance.
3. To evaluate direct cost of TB relapse from government perspective.

1.8 Significance of the Study Findings

The effect of compliance and factors behind it as well as other possible causes for the tuberculosis relapse and its subsequent cost has not been studied in Yemen. The findings of the present study should elucidate the factors that affect relapse of tuberculosis and patients' compliance as well as its consequential economic burden. It should also provide both the community and the government with information on what should be done to ensure compliance to anti-TB treatment.

By identifying factors associated with the relapse and non-compliance, the incidence of the relapse and non-compliance could be decreased thus lead to reduction in patient and society expenditure as well as depletion of limited government resources. In addition, such findings will positively contribute in

achieving the general aims i.e., reducing of tuberculosis relapse rate and enhancing patients' compliance. Through quantifying 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 and patients' compliance in Yemen.

1.9 Summary of the Next Chapters

The following chapters are literature review, methodology, results, discussion and conclusions. The first part of chapter on literature review will provide an overview on relapse of tuberculosis and its related factors. The second part on literature review will present an overview on treatment compliance and its related factors while the third part will deal with a literature review on cost of tuberculosis relapse from the government perspective. In this context, the chapter will explore: 1) economic impact of tuberculosis; 2) application of pharmacoeconomic in TB management; and 3) overview on the literature of tuberculosis cost.

The methodology chapter will provide a description of the study design and brief discussion of human subject protection (confidentiality and ethical issues). Thereafter, the study area, study population, inclusion and exclusion criteria and sample size calculation will be presented. The procedures for data collection and description of the instruments will also be described, followed by a depiction of study variables on relapse and compliance. The chapter will end with exploring the procedures used to estimate the cost of relapse and data management and analysis.

The results chapter reports the results according to the descriptive and inferential statistics that were performed in this study.

Finally, the discussion chapter will provide a discussion on the study findings compared to the existing research literature and also implications of the findings. The last chapter on conclusions will summarize the main study findings, strengths and limitations. The chapter ends with recommendations and suggestions for future studies.