ASSESSMENT OF KNOWLEDGE AND EVALUATION OF TUBERCULOSIS TREATMENT OUTCOMES AMONG GENERAL AND DISEASED POPULATIONS IN NORTH EAST LIBYA

By

Mukhtar A Muftah Solliman

Thesis Submitted In Fulfillment Of the Requirements

for the Degree of Master of Science

March 2012

“In the name of Allah, most Gracious, most Compassionate.”

Read! In the name of your Lord who created, created the human from something which cling Read! And your Lord is Most Bountiful. He who taught (the use of) the pen, taught the human that which he knew not.

The Holy Qur'an; Surah Al-‘Alaq: Verse 1–5

DEDICATION

I would like to dedicate this thesis with lots of love and respect to my wife Aisha Solliman, my lovely daughter Nooral Houda and my son Mohamed Mukhtar who constantly give the moral support to accomplish my dreams. Without whose support, love and care, I would not have realized my dreams in life.

ACKNOWLEDGEMENT

In the Name of Allah, the Most Gracious, the Most Merciful

All praise is due to Allah alone, I praise Him, seek His aid and seek His forgiveness. I testify that there is no God but Allah and that Mohammed (PBUH) is His last messenger. I thank Allah Almighty for giving me the inspiration, patience, time and strength to finish this work. Without Allah's will and mercy I have not been able to achieve all this.

This thesis was the result of the collective effort of a number of important people who directly or indirectly assisted and supported me during my MSc studies. To these people, I owe my gratitude and thanks.

First and foremost, I would like to express my sincere appreciation and gratitude to my main supervisor Assoc. Prof. Dr. Mohamed Azmi Ahmad Hassali who provided the guidance, encouragement and support throughout the completion of this thesis. As a great mentor, Assoc. Prof. Dr. Azmi has also inspired me to think rationally in approaching research problems. I would also like to extend my thanks to my co-supervisor Dr. Mahmoud Sa'di Alhaddad and field supervisor Assoc. Prof. Dr. Mukhtar Mohamed Hadida from Libyan Center for Diseases Control (LCDC) for all their support and guidance in completion of this thesis.

Many thanks and appreciations go to all my friends and colleagues in the Discipline of Social and Administrative Pharmacy (DSAP) for their moral support and help during the course of this research. I would like to specially acknowledge all my dear friends

especially brothers: Dr. Ramadan Al-Kalmi, Fahad Saleem, Dr. Imran Masood, Muhammad Atif, Dr. Harith Al-Qazaz, Alamin Hassan, Mohammed Awad, Mohammed Al-Shakka and Salawi Abdulelah Ahmad for their constant support, encouragement and love during my stay in Malaysia. You are the best friends I have met in over a decade.

I am also indebted and grateful to Prof. Dr. Abdal Hafeez Aboazaar and staff from of the Libyan Center for Diseases Control (LCDC), Assoc. Prof. Dr. Ahmed Alzerat, Director of Regional Tuberculosis Centre Benghazi, Dr. Awad Bendardef, Director of Quefia Chest Hospital, Mr. Moftah Saifalnaser, Director of Chahat Chest Hospital and Ministry of Health Benghazi (Mr. Farj Almanfi, Mr. Ali Mansor, Mr. Gamal Imari, Mr. Ramadan Hadia, Mr Nagy Almsheety, Mr. Abdallah Azouz, Mr. Maftah Alamare and Hussam Mhana).

I would like to thank to my Brother Mohamed Soliman, Sister Mariem Soliman, my wife Aisha Soliman and my children (Mohamed and Nooral Houda) for their continuous love, patience, encouragement and prayers given during the period of completing this thesis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AFB	Acid-Fast Bacillus
AIDS	Acquired Immune Deficiency Syndrome
ART	Anti-Retroviral Treatment
BCG	Bacillus Calmette Guerin
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CTU	Control Tuberculosis Unit
DNA	Deoxyribonucleic acid
DOTS	Directly Observed Treatment Short course
ELISA	Enzyme linked Immunosorbent Assay
EPTB	Extra Pulmonary Tuberculosis
ESR	Erythrocyte Sedimentation Rate
ETH	Ethambutol
WHO	World Health Organization
HIV	Human Immunodeficiency Virus
INH	Isonicotinylhydrazine (Isoniazide)
MDR	Multidrug Resistance
IUATLD	International Union Against Tuberculosis and Lung Disease
NAP	National AIDS Programme
NTP	National Tuberculosis Programme
PCR	Polymerase Chain Reaction
PTB	Pulmonary Tuberculosis
RIF	Rifampicin
RTC	Regional Tuberculosis Center
SGOT	Serum Glutamate Oxaloacetic Transminase
SGPT	Serum Glutamate Pyruvate Transminase
SM	Streptomycin
TST	Tuberculin Skin Test

LIST OF PUBLICATION

Abstract publications and conference presentations

1 Solliman MM, Hassali MA, Alhaddad MSM, & Hadidan MM. Assessment of knowledge about TB among TB patients in North East Libya. Value in Health 2010. 13(7): A505.

2 Solliman MM, Hassali MA, Alhaddad MSM & Hadidan MM. Assessment of knowledge about Tuberculosis (TB) among Libyan Population in North East Libya. Value in Health 2010. 13(7): A560.

3 Solliman MM, Hassali MA, Shafie AA, Alhaddad MSM, Hadidan MM, Atif M & Saleem F . Treatment outcomes of new smear positive pulmonary tuberculosis patients in North East Libya. Value in Health 2011. 14(7): A498.

4 Solliman MM, Hassali MA, Shafie AA, Alhaddad MSM, Hadidan MM & Saleem F. Comparison of knowledge about tuberculosis among Libyan and non Libyan TB patients in North East Libya. Value in Health 2012

5 Solliman MM, Hassali MA, Shafie AA, Alhaddad MSM, Hadidan MM & Saleem F. Assessment of knowledge about tuberculosis among Libyan and non Libyan populations in north east Libya. Value in Health 2012

6 Solliman MM, Hassali MA, Shafie AA, Alhaddad MSM, Hadidan MM2& Saleem F. Assessment of knowledge regarding Tuberculosis (TB) among general population in north east Libya. Value in Health 2012

Publications

1 Mukhtar A Solliman, Mohamed Azmi Hassali, Mahmoud Al-Haddad, Mukhtar M. Hadida, Fahad Saleem, Muhammad Atif and Hisham Aljadhey. Assessment of Knowledge towards Tuberculosis among general population in North East Libya. Journal of Applied Pharmaceutical Science 02 (04); 2012: 24-30.

2 Mukhtar A Solliman, Mohamed A Hassali, Mahmoud Sadi Al-Haddad, Syed Azhar Syed Sulaiman, Asrul A Shafie, Muhammad Atif and Fahad Saleem. Treatment outcomes of new smear positive pulmonary tuberculosis patients in North East Libya. Latin American Journal of Pharmacy 2012:31(4); 567-73.

PENILAIAN TENTANG PENGETAHUAN DAN NATIJAH RAWATAN TUBERKULOSIS DALAM KALANGAN POPULASI AWAM DAN BERPENYAKIT DI TIMUR LAUT LIBYA

ABSTRAK

Tuberkulosis (TB) masih kekal sebagai penyebab utama kematian dan morbiditi dalam kalangan orang dewasa, dengan anggaran 9 juta kes baru dikesan di seluruh dunia setiap tahun. Libya menghadapi peningkatan secara perlahan dalam prevalans TB dari tahun 2000 hingga 2006, dan ia memerlukan pertimbangan sewajarnya daripada pengamal penjagaan kesihatan untuk mengurus TB secara efektif. Dalam konteks ini, penilaian pengetahuan yang berkaitan TB dalam kalangan populasi umum dan berpenyakit adalah perlu dalam usaha merangka program pencegahan dan penyembuhan kesihatan awam yang efektif. Di samping itu, penilaian natijah rawatan boleh membantu dalam mengenali pasti jurang yang perlu ditangani.

Suatu kajian rentas-silang dijalankan dari 1 Januari 2009 hingga 31 Disember 2009. Kajian ini dibahagikan kepada dua bahagian. Dalam bahagian pertama, satu soal selidik yang mengandungi 32 soalan (yang mencakupi sosiodemografi, penyebab, gejala, penularan / penyebaran, diagnosis, faktor risiko, rawatan dan pencegahan TB) diedarkan kepada peserta kesihatan (yang bersetuju menyertai kajian) dari lima buah

bandaraya di Libya (Benghazi, Almarj, Albayda, Darna and Tobruk). Kedua, soal selidik yang sama juga diedarkan kepada pesakit tuberkulosis pumonari yang baru berdaftar di Quefia Chest Hospital dan Shahat Chest Hospital di Timur Laut Libya. Pada bahagian kedua kajian ini, rekod perubatan bagi semua pesakit tuberkulosis pulmonari yang berdaftar di kedua-dua hospital tersebut dalam tempoh Januari 2007 hingga 31 Disember 2008 diekstrak secara retrospektif untuk menilai natijah rawatan.

Hasil kajian menunjukkan bahawa min skor pengetahuan dalam kalangan populasi awam dan populasi berpenyakit adalah 11.47±3.96, 10.75±4.3 masing-masing. Kerakyatan, pendidikan, pendapatan dan kediaman / residen didapati signifikan dengan skor pengetahuan. Natijah rawatan tuberkulosis dari segi kejayaan dan kegagalannya adalah 58.7% dan 41.3%, masing-masing. Perkadaran kegagalan yang amat tinggi adalah dalam kalangan 'defaulter' (n=90), diikuti 'transferred out' (n=26) dan mati (n=11). Kerakyatan dan pendidikan mempunyai kaitan positif yang sederhana dengan kejayaan rawatan. Sementara itu, lelaki, tinggal di kawasan luar bandar, dan perokok mempunyai perkaitan yang amat negatif. Kerakyatan, jantina, kawasan kediaman, diabetes dan merokok secara signifikan berkaitan dengan kegagalan rawatan, sementara diabetes mempunyai perkaitan yang sederhana negatif. Secara am, pengetahuan tentang TB dalam kalangan populasi yang sihat dan yang berpenyakit adalah tidak mencukupi. Kajian mengenal pasti beberapa jurang dalam kawasan penularan, faktor risiko, diagnosis dan pencegahan tuberkulosis.

Selanjutnya, jurang tersebut adalah predominan dalam kalangan responden bukan rakyat Libya, dtinggal di luar bandar dan yang berpendidikan serta berpendapatan rendah.

Bagi pesakit tuberkulosis pulmonari smer positif, sasaran 85% WHO/IUATLD bagi kejayaan natijah tercapai. Penambahbaikan infrastruktur klinik dan makmal di kawasan terpencil, mendidik 'defaulter' tentang manfaat melengkapkan terapi dan menstratakan orang asing sebagai kumpulan berisiko tinggi boleh meningkatkan kadar kejayaan rawatan. Selanjutnya, program pendidikan khusus hendaklah dibangunkan untuk menyebarluaskan pengetahuan tentang tuberkulosis kepada pesakit dan ahli masyarakat, terutamanya mereka yang tergolong dalam strata yang margiral.

ASSESSMENT OF KNOWLEDGE AND EVALUATION OF TUBERCULOSIS TREATMENT OUTCOMES AMONG GENERAL AND DISEASED POPULATIONS IN NORTH EAST LIBYA

ABSTRACT

Tuberculosis (TB) still remains a leading cause of adult mortality and morbidity with an estimated 9 million new cases detected around the globe annually. Libya has faced gradual increase in the prevalence of TB from 2000 to 2006 and this had posed considerable challenges for the healthcare providers to manage TB timely and effectively. Within this context, assessment of TB related knowledge among general and diseased population is necessary in order to plan effective public health curative and preventive programs. In addition, evaluation of treatment outcomes can further lead to identify gaps that need to be addressed while designing appropriate health based interventions.

A cross sectional study was conducted from 1st January 2009 to 31st December 2009. The study was divided into two sections. For the first section, a pre-validated questionnaire covering 32 questions on the socio-demographics, causes, symptoms, transmission, diagnosis, risk factors, treatment and prevention of TB was administered to 1000 consented healthy participants from five Libyan cities (Benghazi, Almarj, Albayda, Darna and Tobruk). Secondly, the same questionnaire was also administered to newly

register pulmonary tuberculosis patients in Quefia and Shahat Chest Hospitals in North East of Libya. In the second part of this study, medical records of all pulmonary tuberculosis patients registered in Quefia and Shahat Chest Hospitals during January 2007 to December 2008 were extracted retrospectively to evaluate treatment outcomes of pulmonary tuberculosis patients.

The study findings revealed that mean knowledge score among general public and diseased population was 11.47±3.8 and 10.75±4.3 respectively. Nationality, education, income and residency were found significant with knowledge scores. Tuberculosis treatment outcomes in terms of success and failure were 58.7 % and 41.3%, respectively. Highest proportion of failure was among defaulters (n=90), followed by transferred out (n=26) and deaths (n=11). Nationality and education had moderate positive association with treatment success, while males, rural residents and smokers had week negative association. Nationality, gender, area of residence, diabetes and smoking were significantly associated with treatment default while diabetes had moderate negative association. In general, knowledge about TB within the healthy and diseased population was in adequate. The study identified number of gaps in the area of transmission, risk factors, diagnosis and prevention of tuberculosis. Furthermore, these gaps predominated in non Libyans respondents, rural residents and those with lower education and monthly income. For smear positive pulmonary tuberculosis patients, the 85% WHO/IUATLD target for successful outcome

has not been achieved. Improving clinical and laboratory infrastructure in peripheral areas, educating defaulters about benefits of completing therapy and stratifying foreigners as high risk groups could improve treatment success rate. Furthermore, specialized educations programs should be developed to disseminate tuberculosis knowledge to patients and community members, especially for those falling in marginalized strata.

CHAPTER ONE

INTRODUCTION

1.1 Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. It is estimated that one third of world's population is affected with this disease and it causes two million deaths every year (Kherad et al., 2009, World Health Organization, 2006a). Since the mid 80's with the advent of HIV/AIDS, the prevalence of TB has been increasing especially in Sub-Saharan Africa (Okot-Nwang et al., 1993). The incidence of TB among HIV infected patients is 45% and about 50% of HIV infected patients will develop TB in their lifetime (Okot-Nwang et al., 1993). It has been documented that TB situation has worsened over the past two decades in Africa owing to the HIV/AIDS epidemic (Borgdorff et al., 2002). The African region has the highest estimated incidence rate of 356 per 100,000 populations per year (World Health Organization, 2006b). Eighty percent of all cases worldwide occur in Sub-Saharan Africa and South East Asia (Dye et al., 1999). In 2005, it was reported, that there were about 24 new TB cases in Libya (all forms) (per 100,000 populations) (World Health Organization, 2006c). In 2007, incidence rate of TB in Libya was 17 cases (all forms) per 100,000 populations (TB Unit of the WHO Regional Office for Eastern-Mediterranean Region, 2007). However in 2008, incidence rate of TB increased up to 40 cases (all forms) per 100,000 populations (TB Unit of the WHO Regional Office for Eastern-Mediterranean Region., 2008). This increase in incidence rate is possibly a result influx of immigrants from Saharan and Sub-Saharan Africa (World Health Organization, 2007b), where incidence rate for TB is more than 300 cases (all forms) per 100,000 populations (World Health Organization, 2006c). The task of TB management is quite difficult for patients and providers because of its longer duration

(Bass Jr et al., 1994). In order to combat treatment challenges, worldwide, Directly Observed Treatment Short Course Strategy (DOTS) was adopted in mid 1990s which formed the basis of TB control (World Health Organization, 2009). National Tuberculosis Program (NTP) of Libya adopted DOTS program in 1998 (World Health Organization, 2007b). Benghazi, Tripoli and Sebha are capital cities of Eastern, Western and Southern regions of Libya, respectively and each of these cities has a Regional Tuberculosis Control Center (RTC). Four TB hospitals are located in Benghazi, Shahat, Tripoli and Misurata. A total of 24 Peripheral Tuberculosis Control Centers (PTCC) are located in various peripheral areas of the country to assist patients in completion of their treatment (Elghoul MT, 1981). Global targets for TB control were set by World Health Assembly (WHA) in 1991 (Dye, 2006). According to these targets, case detection for new sputum smear positive TB must be at least 70% with a cure rate not less than 85% (World Health Organization, 1991). Achieving these goals requires the active participation of the community by creating awareness on the causes, symptoms, management, preventive measures, and information on the availability of services.

1.2 Problem Statement

World Health Organization provided evidence of a gradual increase in the prevalence of TB in Libya from 2000 to 2006. Moreover global target for TB control was not achieved (World Health Organization, 2006c, World Health Organization, 2007c). African region has the highest rate per capita of TB incidence in the World, and most of the worst affected countries are located in Sub-Saharan Africa (Kim, 2002). As a matter of fact, Libya is nearest to Sub-Sahara countries and thus having

greater chances of TB outbreak (World Health Organization, 2007c). Higher incidence of TB might be consequence of increase in legal or illegal immigration from Africa across southern border from Sub-Saharan Africa or lack of appropriate knowledge of TB in public (World Health Organization, 2007c). Existing literature do not provide any information on the factors that significantly affect successful TB treatment outcomes. Furthermore, no data is available to provide an insight of patient's and general public knowledge about TB in Libya (World Health Organization, 2011). Therefore, the aim of the present study is to evaluate the factors significantly affecting TB treatment outcomes as well as to assess the TB knowledge in general public and TB patients. Findings of this study will enable DOTS providers and policymakers to devise appropriate interventions to shape NTP of Libya according to current requirements.

1.3 Rational of the Study

Libya, like many other countries, uses the Tuberculosis Control Programme (TCP) for proper patient registration and reporting (World Health Organization, 2007b) World Health Organization has reported that no studies have been conducted in Libya focusing on knowledge of TB among general public and TB patients (World Health Organization, 2006a, World Health Organization, 2011). Knowledge about any disease is fundamental to optimize patients treatment and to improve their quality of life (Jaramillo, 2001). Therefore, findings of this study will serve as a baseline data about knowledge of TB among general public and TB patients in Libya. This will allow health care professionals and DOTS providers to shape a comprehensive awareness program

for awareness of TB. Secondly, to-date no study has explored TB treatment outcomes according to World Health Organization Guidelines. Likewise, no data is available on factors that significantly affect treatment outcomes. Therefore, current study will provide an insight of factors that significantly affect treatment outcomes.

1.4 Conceptual Framework

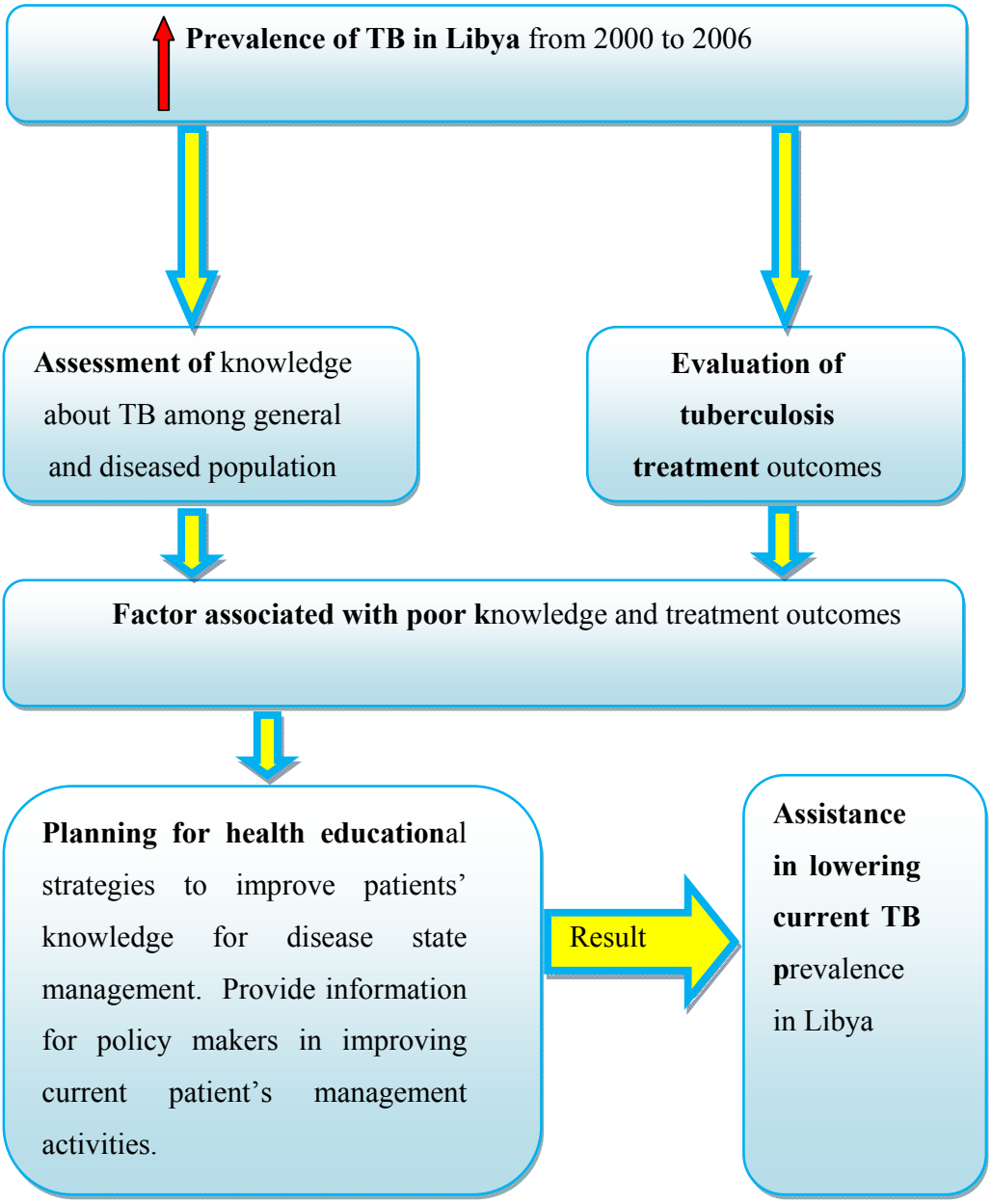

Figure 1.1: Conceptual Framework of the Study

1.5 Significance of the Study

Most difficult task of TB treatment is to convince patients to take their medications regularly without any interruption (Munro et al., 2007). For successful treatment outcomes, patient co-operation is essential (Sumartojo, 1993). Lack of patient motivation can be associated with in adequate knowledge about TB (Demissie et al., 2002). Poor knowledge may lead to treatment failure, relapse and default from treatment (Dodor and Afenyadu, 2005). Moreover, these adverse consequences not only significantly affect patients but also their families and society. This study is the first of its kind in North East Libya for assessment of TB knowledge among general public and TB patients. Moreover, the success of DOTS depends on timely case detection and early medical management. To date, Libya has not achieved 85% treatment success rate set by WHO (World Health Organization, 2011). Therefore, results of this study would provide a baseline data to the decision makers for appropriate management of TB in Libya. Some of the possible policy implications can be:

- Proportion of cases with successful outcome could be improved by provision of modern health care facilities at peripheral areas.
- There is strong need for awareness among health care professionals and immigration authorities to ensure treatment completion of foreigners.
- Adequate professional commitment and expertise of health care professionals can result in improvement of treatment success rates.

1.6 Study Objectives

The objectives of this study are:

1) To assess the level of knowledge of the Libyan population concerning etiology, mode of transmission, diagnosis, risk factors, treatment and prevention of TB.
2) To assess the knowledge of TB patients concerning etiology, mode of transmission, diagnosis, risk factors, treatment and prevention of TB.
3) To evaluate treatment outcomes of newly diagnosed pulmonary tuberculosis patients (PTB) in two TB hospitals of North East Libya.

1.7 Thesis Overview

This thesis is composed of 6 chapters, including the present chapter. Each chapter's brief overview is outlined below

1.7.1 Chapter One

This chapter provides a general overview of the research problem. It also presents the general flow of the whole research project.

1.7.2 Chapter Two

Chapter two frames the literature review for the thesis. The chapter reflects both the diversity of issues that are addressed at global level concerning the management and social aspects of TB. This chapter also highlights the need to concentrate on the neglected aspects of TB in Libya.

1.7.3 Chapter Three

This chapter describes the methodology and findings from quantitative survey designed to assess knowledge of TB in general public in northern states of Libya. This chapter is divided into two parts. Part I mainly describes study design and the steps adopted to develop a valid questionnaire for assessment of TB knowledge and second part presents findings and discussion.

1.7.4 Chapter Four

This chapter describes the methodology and findings from quantitative survey designed to evaluate knowledge of tuberculosis among newly diagnosed TB patients in two TB hospitals in North East Libya. This chapter also provides an overview of methodological approaches adopted to attain this specific objective.

1.7.5 Chapter Five

This chapter describes treatment outcomes of TB in two hospitals of North East Libya during 2007 and 2008. This chapter also describes the factors which are significantly associated with successful treatment outcomes. This chapter also highlights the factors significantly associated with treatment default.

1.7.6 Chapter Six

Chapter six draws the thesis to conclusion and suggested recommendations for further research.

CHAPTER TWO

LITERATURE REVIEW

2.1 Global Epidemiology of Tuberculosis

Tuberculosis is an airborne disease caused by the *Mycobacterium tuberculosis* and is still one of the most deadly, and disabling diseases in the developing world (Beltz, 2011, Borgdorff et al., 2002, Dye et al., 2005). The WHO estimates that approximately one-third of the global community is infected with *Mycobacterium tuberculosis* (Dye et al., 2005). Worldwide, in 1995 there were about 9 million new cases of TB with 3 million deaths every year (Ernesto Montoro and Rodolfo Rodriguez, 2007). In 2007, annual incidence rate of TB raised up to 9.27 million new cases from 9.24 million in 2006 (Glaziou et al., 2009). Asia (55%) and Africa (31%) shared the maximum burden, with small proportions of cases in the Eastern Mediterranean Region (6%), the European Region (5%) and the Region of the Americas (3%) (Glaziou et al., 2009). Current trends suggest that TB will be among the ten leading causes of global disease burden in the year 2020 (Murray and Lopez, 1997). The five countries that rank first to fifth in terms of total numbers of cases in 2007 are India (2.0 million), China (1.3 million), Indonesia (0.53 million), Nigeria (0.46 million) and South Africa (0.46 million). African region has the highest estimated incidences rate (356/100,000 populations) (Dye, 2006, World Health Organization, 2006c). The World Health Organization has reported that incidence rate in Sub-Saharan Africa is nearly twice as that of the South-East Asia (World Health Organization, 2011).

2.2 Epidemiology of Tuberculosis in Libya

TB was documented as prevalent in 1887 in the coastal district western region of Libya, but it was found hardly to exist in the countryside (Elghoul MT, 1981). In 1912, 88 cases were reported in the city of Tripoli, and few cases in other parts of the western region. An investigation in 1930 in 72 different places in southern region revealed only two cases (Elghoul MT, 1981). The incidence of TB in Libya increased with the industrial revolution in 1960. Due to this revolution, people especially from southern region moved into cities, particularly in capital city, Tripoli. As a disease prevention strategy in 1953, Bacille Calmette-Guérin (BCG) vaccination campaign was conducted throughout the country (Elghoul MT, 1981). In 2007, incidence rate of TB in Libya was 17 cases (all forms) per 100,000 populations (World Health Organization, 2007b). However in 2008, incidence rate of TB increased up to 40 cases (all forms) per 100,000 populations (World Health Organization, 2007d). This increase in incidence rate is possibly a result of increasing immigrants from Saharan and Sub- Saharan Africa, where incidence rate for TB is more than 300 cases (all forms) per 100, 000 population (World Health Organization, 2008b). Incidence of Multi-drug resistant TB is 2.6% among the new cases and 39% among re-treatment cases (World Health Organization, 2006d). Table 2.1 shows the case detection of new smear positive cases during 1971 to 2008 (National Center for Disease Control Libya, 2008).

Table 2.1: Case detection of new smear positive pulmonary TB patient's from 1971 to 2008

Years	Libyans n(%)	Non Libyans n(%)	Total
1971	700 (90.4)	74 (9.6)	774
1972	920 (91.6)	84 (8.4)	1004
1973	964 (84.6)	176 (15.3)	1140
1974	840 (71.2)	341 (28.9)	1181
1975	715 (61.2)	423 (37.2)	1138
1976	657 (65.4)	347 (34.6)	1004
1977	739 (67.7)	352 (32.3)	1091
1978	507 (63.7)	289 (36.3)	796
1979	475 (64.8)	258 (35.2)	733
1980	446 (63.5)	256 (36.5)	702
1981	490 (57.4)	363 (42.6)	853
1982	427 (55.2)	346 (44.8)	773
1983	367 (55.3)	297 (44.7)	664
1984	318 (59.7)	215 (40.3)	533
1985	345 (69.1)	154 (30.9)	499
1986	320 (69.4)	141 (30.6)	461
1987	331 (68.1)	155 (31.9)	486
1988	273 (62.3)	165 (37.7)	438
1989	252 (54.3)	212 (45.7)	464
1990	258 (53.9)	221 (46.1)	479
1991	262 (49.8)	264 (50.2)	526
1992	251 (45.9)	296 (54.1)	547
1993	274 (45.7)	325 (54.3)	599
1994	290 (48.7)	305 (51.3)	595
1995	345 (55.1)	281 (44.9)	626
1996	330 (64.1)	185 (35.9)	515
1997	394 (62.8)	233 (37.2)	627
1998	463 (62.9)	273 (37.1)	736
1999	457 (56.9)	346 (43.1)	803
2000	439 (63.7)	250 (36.3)	689
2001	436 (64.5)	240 (35.5)	676
2002	436 (62.8)	258 (37.2)	694
2003	509 (66.6)	255 (33.4)	764
2004	573 (65.7)	299 (34.3)	872
2005	615 (71.5)	245 (28.5)	860
2006	544 (73.02)	201 (26.98)	745
2007	601 (77.8)	171 (22.2)	772
2008	621 (71.3)	250 (28.7)	871

Source: (National Center for Disease Control Libya, 2008)

2.3 Pathogenesis of Tuberculosis

Primary site of tuberculosis infection is pulmonary alveoli, where *Mycobacterium tuberculosis* invades and replicates within the endosomes of alveolar macrophages (Kumar et al., 1992, Houben et al., 2006). The primary site of infection in the lungs is called the Ghon focus, and is generally located in either the upper part of the lower lobe, or the lower part of the upper lobe (Kumar et al., 1992). Bacteria are picked up by dendritic cells, which do not allow replication, although these cells can transport the bacilli to local (mediastinal) lymph nodes. TB can spread to other tissues and organs through the bloodstream where secondary TB lesions can develop in other parts of the lung (particularly the apex of the upper lobes), peripheral lymph nodes, kidneys, brain, and bone (Kumar et al., 1992, Herrmann and Lagrange, 2005). Each and every part of the body can be affected by TB though it rarely affects the heart, skeletal muscles, pancreas and thyroid (Agarwal et al., 2005).

TB is an inflammatory condition with formation of granuloma. Macrophages, T-lymphocytes, B-lymphocytes and fibroblasts aggregate to form a granuloma. Lymphocytes surround the infected macrophages. Cytokines such as interferon gamma, are secreted by T-lymphocytes which activates macrophages to destroy the bacteria with which they are infected (Kaufmann, 2002). Cytotoxic T cells can also directly kill infected cells, by secreting perforin and granulysin (Houben et al., 2006). When lung tissues are damaged bacteria get access to blood stream and spread through the body and set up many foci of infection. There they appear as tiny white tubercles in the tissues. This severe form of TB disease is most common in infants and the elderly and is

called miliary tuberculosis and has a fatality rate of approximately 20%, even with intensive treatment (Kim et al., 2003). In pulmonary tissue, destruction and necrosis are balanced by healing and fibrosis (Grosset, 2003). Affected tissue is replaced by scarring and cavities filled with cheese-like white necrotic material. During active disease, some of these cavities are joined to the air passages bronchi. When a person coughs with such condition he/she disperse droplets in air along with number of live bacteria (Cole and Cook, 1998).

2.4 Transmission of Tuberculosis

Patient of pulmonary tuberculosis (PTB) expel infectious aerosol droplets ranging from 0.5 to 5 μm in diameter. A single sneeze of infected patient can release up to 40,000 droplets (Cole and Cook, 1998). Each one of these droplets may have the capability of transmitting the disease. However, transmission is limited to patients with active PTB (Robbins et al., 2010). Since the infectious dose of *Mycobacterium tuberculosis* is very low, therefore, inhaling less than ten bacteria may cause an infection in healthy volunteer (Nicas et al., 2005, Behr et al., 1999). The probability of transmission from one person to another depends upon the number of infectious droplets expelled by a carrier; the effectiveness of ventilation, the duration of exposure, and the virulence of the *Mycobacterium tuberculosis* strain, people with prolonged, frequent, or intense contact with infected individuals are particularly at high risk. It was observed that a single person with active TB have the threatening ability to infect 10–15 people per year (World Health Organization, 2011). TB can also be transmitted by eating meat infected with *Mycobacterium bovis* (Majoor et al., 2011). Some of the higher risk

groups are; smokers, intravenous drug abusers , alcoholics, diabetics, residents and employees of high-risk congregation settings, people with poor socioeconomic characteristics, malnourished, patients taking corticosteroids and patients who are immune-compromised (Behr et al., 1999).

2.5 Diagnosis of Tuberculosis

A complete medical evaluation for TB must include a medical history, a physical examination, a chest X-ray, microbiological smears, and cultures. Smear test alone or smear and culture tests are helpful in early detection of TB (Arenas et al., 2008, Zamarioli et al., 2009). New TB tests are being developed that offer the hope of cheap, fast and more accurate TB testing. These include polymerase chain reaction (Balasingham et al., 2009), detection of bacterial Deoxyribonucleic acid (DNA), assays to detect the release of interferon gamma in response to mycobacterium proteins such as ESAT-6 (Nahid et al., 2006) and Enzyme Linked Immunosorbent Assay (ELISA) (Chou et al., 2009).

2.5.1 Medical History

The medical history includes obtaining the symptoms of pulmonary TB such as history of cough for three or more weeks, chest pain, and hemoptysis. Systemic symptoms include low grade remittent fever, chills, night sweats, appetite loss, weight loss, easy fatigability (Cole and Cook, 1998). Medical history also includes prior TB exposure, infection or past history of TB treatment or any other high risk behavior like smokers, alcoholic, malnourished or immune-compromised patients.

TB should be suspected when a persistent respiratory illness in an otherwise healthy individual does not respond to regular antibiotics (Cole and Cook, 1998).

2.5.2 Radiography

Radiographic procedures for diagnosis of PTB are often based on abnormal chest radiographic findings in a patient with respiratory symptoms. Although the "classic" picture is that of upper lobe disease with infiltrates and cavity virtually, but patients can never be diagnosed of TB. However, chest radiographs may be used to rule out the possibility of PTB in a person who has a positive reaction to the tuberculin skin test and has no symptoms of disease (Robbins et al., 2010). In addition, a diographic pattern may be seen. In the era of AIDS, no radiographic pattern can be considered pathogenomonic (Mariani, 2000). Abnormalities on chest radiographs may be suggested.

2.5.3 Microbiological studies

A definitive diagnosis of TB can only be made by culturing *Mycobacterium tuberculosis* from a specimen taken from the patient's sputum. Specimens may also include pus, Cerebrospinal fluid (CSF) or biopsied tissue (Robbins et al., 2010). However, a presumptive diagnosis is commonly based on finding of Acid-fast bacilli (AFB) on microscopic examination of a diagnostic specimen such as a smear of expectorated sputum or of tissue. For patients with suspected PTB, usually three sputum samples are collected early in the morning on different days (World Health Organization, 2009). In cases where there is no spontaneous sputum production, a

sample can be induced, usually by nebulizer inhalation of a saline (Brown et al., 2007).

2.5.4 Tuberculin Skin Test (TST)

Tuberculin Skin Test (TST), Mantoux skin test is of limited value in the diagnosis of active TB because of its low sensitivity and specificity. False-negative reactions are common in immunosuppressed patients and in those with overwhelming TB. Positive reactions can be obtained when patients have been infected with *Mycobacterium tuberculosis* but do not have active disease or persons who have undergone Bacilli Calmette-Guerin (BCG) vaccination. In the absence of a history of BCG vaccination, a positive skin test may provide additional support for the diagnosis of TB in culture-negative cases (Huebner et al., 1993).

2.5.5 Extra Pulmonary Tuberculosis (EPTB)

TB of organs other than the lungs is called extra pulmonary tuberculosis. Mainly it includes the peripheral lymph nodes, abdomen, the pleura (TB pleurisy), skin, joints, bones, and the brain. The diagnosis of EPTB Tuberculosis is often difficult compared with PTB due to the low sensitivity of the diagnostic methods for the disease. Usually specimen samples from affected organs are taken for histopathological (HPE) examinations by pathologists (Sharma and Mohan, 2004).

2.6 Treatment of Tuberculosis

TB is a curable infectious disease but longer duration of its treatment is one of greatest barrier to treatment. The aim of treatment is not only to cure the patients, but

also to prevent mortality, relapse and transmission of disease (World Health Organization, 2009).

2.6.1 History of Tuberculosis Treatment

Before discovering specific antibiotics for TB treatment, the mortality of patients with pulmonary disease was about 50%. By the end of 1980's, TB was 98% curable. The present TB chemotherapy is one of the most fabulous achievements in the field of medicine. The first trials of TB treatment began when Robert Koch (1882) discovered a staining technique that enabled him to see *Mycobacterium tuberculosis*. The discoveries of streptomycin in 1944, para-amino salicylic acid in 1946, and isoniazid in 1952 led to the first effective cure for TB (Leung, 1999).

2.6.2 Treatment of Latent Tuberculosis Infection (LTBI)

Patients of LTBI are usually identified by TST. In order to prevent the development of active disease in the future, patients should be treated with isoniazid (10 mg/kg/day or, at most, 300 mg/day) for six to nine months (Castelo Filho et al., 2004). Although, such treatment reduces the risk of active TB but it does not protect the patient from exogenous exposure. Candidates for treating latent TB infection are those included in high risk groups (Jasmer et al., 2002).

2.6.3 Treatment of Active Tuberculosis Infection

Standard short course regimens are divided into an Initial intensive Phase (IP) or bactericidal phase and Continuation Phase (CP) or sterilization phase. Through the initial phase, the greater part of the tubercle bacilli are destroyed; symptoms are

resolved and generally the patient become noninfectious. The continuation phase is necessary to remove persisting *Mycobacterium* and avoid relapse (Yew, 2006).

Isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin are listed as first line anti TB drugs. Table 2.2 shows available dosage forms and daily dose of each drug calculated on patient body weight.

Table 2.2: Daily dose and available dosage forms of first line anti-tuberculosis drugs

Drug	Dosage form	Available strengths	Daily dose	Three times per week
Isoniazid	Tablet	100 mg, 300 mg	5 mg/kg (max.300 mg)	10 mg (max.900 mg)
Rifampicin	Tablet or capsule	150 mg 300 mg	10 mg/kg (max.600 mg)	10 mg (max.900 mg)
Pyrazinamide	Tablet	400 mg	15-30 mg/kg	35 mg
Ethambutol	Tablet	100 mg,	15-25 mg/kg	30 mg
Streptomycin	Powder for injection in vial	400 mg 1 g	12-18 mg/kg	15 mg (max.1000 mg)

Source: (World Health Organization, 2009)

Like other drugs, anti TB drugs also produce adverse effects which are categorized as minor and major adverse drugs. Table 2.3 shows symptom base management of these adverse effects.

Table 2.3: Symptom based approach to managing side effects of anti TB drugs side-effects

Symptom based approach to managing side effects of anti TB drugs Side-effects	Drug(s)probably responsible	Management
Major	Stop responsible drug(s) and refer to clinician urgently	
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin
Minor	Continue anti-TB drugs, check drug doses	
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advice patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50–75 mg daily (3)
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration (3)

Source: (World Health Organization, 2009)

2.6.4 Standardized Treatment Regimen

Standardized treatment means that all patients in defined group receive the same treatment regimen (World Health Organization, 2009). Table 2.4 shows standardized treatment regimen for newly diagnosed TB patients.

Table 2.4: Standard regimens for new TB patients

Initial intensive phase of treatment	Continuation phase of treatment
2 months HRZE[a]	**4 months HR**
2 months HRZE	**4 months HRE[b]**
2 months HRZE	**4 months $(HR)_3$[c]**

[a] WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative PTB or EPTB who are known to be HIV-negative. In tuberculosis meningitis, ethambutol should be replaced by streptomycin.

[b] In settings where the level of isoniazid resistance among new TB cases is high and isoniazid susceptibility testing is not done (or results are not available) before the continuation phase begins.

[c] Three times weekly for four months provided that each dose is directly observed. H = isoniazid, R= rifampicin, Z = pyrazinamide, E= ethambutol, S = streptomycin (World Health Organization, 2009).

2.6.5 Re-treatment of TB

Previously treated TB patients include those patients treated as new cases for more than one month who are now smear or culture positive (failure, relapse, return after default). Re-treatment cases have a higher likelihood of drug resistance, which may have been acquired through inadequate prior chemotherapy. Standard treatment regimen for re-treatment case is as follows; 2HRZES/1HRZE/5HRE. This standardized regimen can cure patients excreting bacilli still fully sensitive to the drugs and those excreting bacilli resistant to isoniazid and / or streptomycin (World Health Organization, 2009).

2.6.6 Treatment of Resistant TB

Multi-drug resistant Tuberculosis (MDR-TB) is defined as TB that is resistant at least to isoniazid and rifampicin. In designing the country's MDR-TB treatment component and integrating it into the national program, NTP managers are strongly encouraged to make full use of the Green Light Committee (GLC). The GLC is a subgroup of the MDR-TB Working Group of the Stop TB Partnership, and an advisory body of WHO that promotes access to (and monitors the use of) quality-assured, life-saving MDR-TB treatment (World Health Organization, 2009).

For MDR treatment, anti-TB drugs are grouped according to efficacy, experience of use and drug class (Table 2.5). All the first-line anti-TB drugs are in Group 1, except streptomycin, which is classified with the other, injectable agents in Group 2. All the drugs in Groups 2–5 (except streptomycin) are second-line, or reserve drugs (World Health Organization, 2008b).

Table 2.5: Groups of drugs to treat MDR-TB

Group	Drugs (abbreviations)
Group 1 First-line oral agents	Pyrazinamide (Z)
	Ethambutol (E)
	Rifabutin (Rfb)
Group 2 Injectable agents	Kanamycin (Km)
	Amikacin (Am)
	Capreomycin (Cm)
	Streptomycin (S)
Group 3 Fluoroquinolones	Levofloxacin (Lfx)
	Moxifloxacin (Mfx)
	Ofloxacin (Ofx)
Group 4 Oral bacteriostatic second-line agents	Para-aminosalicylic acid (PAS)
	Cycloserine (Cs)
	Terizidone (Trd)
	Ethionamide (Eto)
	Protionamide (Pto)
Group 5 Agents with unclear role in treatment of drug resistant-TB	Clofazimine (Cfz)
	Linezolid (Lzd)
	Amoxicillin/clavulanate (Amx/Clv)
	Thioacetazone (Thz)
	Imipenem/cilastatin (Ipm/Cln)
	High-dose isoniazid (high-dose H)b
	Clarithromycin (Clr)

High-dose isoniazid is defined as 16–20 mg/kg/day. Some experts recommend using high-dose isoniazid in the presence of resistance to low concentrations of isoniazid (>1% of bacilli resistant to 0.2 μg/ml but susceptible to 1 μg/ml of isoniazid), whereas isoniazid is not recommended for high-dose resistance (>1% of bacilli resistant to 1 μg/ml of isoniazid) (World Health Organization, 2009) (World Health Organization, 2008b).

2.7 Directly Observed Therapy Short Course (DOTS)

1. Direct observed treatment short course (DOTS) can improve adherence to treatment as it requires the patients to swallow their medications under direct observation of DOTS providers. Around 10 million infectious patients have been successfully treated under the DOTS programmes since it was first introduced on a global scale in 1995.

   Five fundamental principles of DOTS are as follows:

   i. Political commitment and resources

   ii. Accurate diagnosis by AFB smear-positive

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

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

   v. Monitoring of the outcome of the patients (World Health Organization, 2009).

2- In 2004, 183 countries and territories implemented DOTS strategy and 83% of the world's population lived in DOTS-covered countries in the end of 2004. 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 (Ernesto Montoro and Rodolfo Rodriguez, 2007). Throughout the world, case detection rate by DOTS increased from 11% in 1995 to approximately 45% by 2003, and