FACTORS INFLUENCING DELAYED TREATMENT AMONG SMEAR POSITIVE PULMONARY TUBERCULOSIS PATIENTS

by

DR NOOR HASHIMAH BINTI ABDULLAH

Dissertation Submitted In
Partial Fulfillment Of The
Requirements For The Degree Of
Master Of Community Medicine
(Epidemiology and Biostatistics)

UNIVERSITI SAINS MALAYSIA
2006

ACKNOWLEDGEMENTS

Bismillahirrahmanirrahim

Praise to Allah s.w.t, the most compassionate and most merciful, whose blessing has helped me through the entire completion of this paper. I would like to express my deepest gratitude and thank to the following individuals who helped me during the preparation of this dissertation and during the course to pursue the Master of Medicine (Community Medicine) in School of Medical Sciences, Universiti Sains Malaysia, Kelantan.

- My supervisor, Assoc. Prof. (Dr) Syed Hatim Noor @ Nyi Nyi Naing, Coordinator of Biostatistics and Research Methodology Unit, USM for his support, encouragement, valued advice, comments, suggestions and contribution of his time throughout the research and completion of this dissertation.
- Assoc. Prof. (Dr) Muhammad Rusli Abdullah, lecturer in the Department of Community Medicine and Dr. Che Wan Aminud-Din Hashim, lecturer in the Department of Medicine as my co-supervisors for their support and commitment.
- Dr. Wan Mansor bin Hamzah (State Epidemiologist-Communicable disease) and Dr.Hani bt. Hussin (State Epidemiologist-Tuberculosis and Leprosy) for their support.
- Dr. Rosemi Saleh, Physician and Head of Medical Department, Hospital Kota Bharu and all the Medical Officers of Health in charge of Kota Bharu, Tumpat, Bachok and Pasir Mas districts for their permission and full cooperation for me to conduct this study.
- Assoc. Prof. (Dr) Mustaffa Musa, Head of Immunology Department.

- Dr Mohd Ayub Saddiq, the lecturer in PPSG for his advice and guidance on the statistical analysis.
- Members of State Tuberculosis Organizer Team. Mr. Hj. Yusof Abbas (Tuberculosis state co-ordinator), Mrs. Azimah Abdullah, Mrs. Tuan Jah bt. Tengku Bongsu and Mr. Tengku Mizan Tengku Wok for their cooperation.
- Mr. Abdul Aziz bin Zakaria, Mr. Mohd. Rashid bin Ismail, Mr. Azman bin Mohd Noor and Mr. Mat Zain bin Yaacob, the health inspectors in charge of Disease Control Unit-Tuberculosis and Leprosy for respective district and other Ministry of Health staff who were involved in the research direct or indirectly.
- All the lecturers, colleagues and all staff in the Department of Community Medicine.
- Muhammad Rusydi Abdul Malek, my beloved husband, my mother and my family who gave a great support and spared their time for the success of the dissertation and the course.
- My friends, Mr. Mohd Hilmi Abu Bakar, Ms. Nur Zawanie Zakaria, Mr. Wan Muhd Lokman Wan Mustapha for their assistance and support.
- Last but not least all the patients who were willing to give their cooperation to participate in this study.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS, ABBREVIATIONS AND NOMENCLATURES.

AFB	-	Acid Fast Bacilli
AIDS	-	Acquired Immunodeficiency Syndrome
BCG	-	Bacillus Calmette-Guerin
CDC	-	Center of Disease Control, Atlanta, USA
CXR	-	Chest X-ray
DNA	-	Deoxyribonucleic Acid
DOTS	-	Directly Observed Treatment, Short-course
ELISA	-	Enzyme-linked Immunosorbent Assay
FDA	-	Food and Drug Administration
HIV	-	Human Immunodeficiency Virus
INF	-	Interferon-gamma
INH	-	Isoniazid
MDGs	-	Millennium developmental goals
MMWR	-	Morbidity & mortality weekly report
MOH	-	Ministry of Health, Malaysia
NTP	-	National Tuberculosis control Programme
PPD	-	Purified Protein Derivatives
PTB	-	Pulmonary Tuberculosis
PZA	-	Pyrazinamide
QFT	-	QuantiFERON
T.U	-	Tuberculin Unit

TST	-	Tuberculin Skin Test
TB	-	Tuberculosis
TBIS	-	National Tuberculosis Information system
TC1	-	Treatment Center One
TC2	-	Treatment Center Two
T/CM	-	Traditional and Complementary medicine
WHO	-	World Health Organization

ABSTRAK

TAJUK

Faktor yang mempengaruhi kelewatan memulakan rawatan di kalangan pesakit tuberculosis (TB) berjangkit.

PENGENALAN

TB masih merupakan penyakit yang memberi cabaran besar kepada kesihatan komuniti di dunia dan khasnya di Malaysia. Kelambatan memulakan rawatan dapat meningkatkan mobiditi penyakit, kematian dan transmisi penyakit TB. Kajian ini bertujuan untuk mengetahui prevalen pelbagai jenis kelewatan (kelewatan pesakit, kelewatan perkhidmatan kesihatan, kelewatan mendiagnosa, kelewatan dalam inisiasi rawatan dan keseluruhan kelewatan dalam memulakan rawatan TB) dan faktor-faktor yang mempengaruhi kelewatan pesakit dan kelewatan perkhidmatan kesihatan.

KAEDAH

Kajian hirisan lintang telah dijalankan dari bulan Oktober 2004 hingga ke bulan Jun 2005 ke atas 178 orang pesakit TB berjangkit di empat daerah di Kelantan (Kota Bharu, Tumpat, Bachok dan Pasir Mas). Semua pesakit yang memenuhi ciri-ciri kajian dan memberikan persetujuan ditemuramah disebabkan kekurangan jumlah pesakit untuk memenuhi keperluan bilangan sampel. Borang kaji selidik digunakan untuk menemuramah pesakit manakala maklumat keputusan makmal diperolehi daripada rekod pesakit.

KEPUTUSAN

Median dan 'interquartile range' kelewatan pesakit, kelewatan perkhidmatan kesihatan, kelewatan mendiagnosa, kelewatan inisiasi dan keseluruhan kelewatan rawatan didalam hari masing-masing adalah 30.0(76.00), 7.0(14.50), 3.0(4.00), 3.0(4.00) and 64.0(90.25). Prevalen dan 95%CI bagi kelewatan yang melebihi had pula; kelewatan pesakit, kelewatan perkhidmatan kesihatan, kelewatan mendiagnosa, kelewatan inisiasi dan keseluruhan kelewatan rawatan masing-masing adalah 46.6%(39.3, 53.3), 45.5%(38.2, 52.8), 48.3%(41.0,55.6), 37.6%(30.5,44.8), 61.8% (54.7,68.9). Analisis melalui 'multiple logistic regression' mendapati faktor yang mempengaruhi kelewatan pesakit melebihi had adalah faktor umur (OR: 3.88; 95%CI: 1.35, 11.18; p= 0.012), jarak rumah pesakit ke fasiliti kerajaan pertama dilawati (OR: 3.98; 95%CI: 1.56, 10.15; p= 0.004), melawati pengamal perubatan tradisional (OR: 10.51; 95%CI, 1.80, 55.39; p=0.006), melawati sektor perubatan swasta (OR: 0.24, 95%CI: 0.09, 0.60; p= 0.002) dan pengaruh stigma (OR: 4.81; 95%CI: 1.59, 14.60; p=0.006). Faktor-faktor yang didapati signifikan berkaitan dengan kelewatan perkhidmatan kesihatan melebihi had pula adalah keputusan awal sapuan kahak yang negative (OR:14.48; 95%CI: 2.30, 91.34; p=0.004), peningkatan jumlah lawatan ke fasiliti kerajaan (OR: 4.99 95%CI: 2.76, 9.03; p= <0.001) dan jenis perkhidmatan kerajaan yang dilawati (OR: 5.78; 95%CI: 1.58, 21.11; p= 0.008).

KESIMPULAN

Kajian ini mendapati bahawa terdapat kelewatan di dalam mengesan kes-kes TB di Kelantan. Meningkatkan kesedaran melalui kempen pengajaran kesihatan dan promosi kesihatan berkenaan dengan gejala-gejala penyakit TB, kebolehsembuhannya dan kesediaadaan fasiliti-fasiliti kerajaan dalam menangani penyakit TB mungkin mampu

memendekkan kelewatan pesakit mendapatkan rawatan. Kakitangan-kakitangan kerajaan dan swasta perlu disedarkan tentang kepentingan awal membuat diagnosa dan memulakan rawatan. Pengamal Kesihatan traditional dan komplementari perlu bekerjasama dan berintergrasi dengan sektor kesihatan swasta dan kerajaan dalam menyumbang kepada sistem kesihatan negara ini.

ABSTRACT

TOPIC

Factors influencing delayed treatment among smear positive pulmonary tuberculosis.

INTRODUCTION

TB remains a great challenge to public health in Malaysia and worldwide. Delay in treatment commencement can result in significant increase morbidity, mortality and transmission. Hence this study is aimed to determine the prevalence of various delays (patient, health service, diagnosis, initiation and total delay) and to identify the factors influencing the patient delay and health service delay.

METHOD

A crossectional study was done from October 2004 to June 2005 among 178 smear positive pulmonary TB patients in four districts in Kelantan (Kota Bharu, Tumpat, Bachok and Pasir Mas). All patients who fulfilled the inclusion and exclusion criteria and gave consent were recruited due to limited number of patients. Interviewer guided questionnaire was administered and medical record was reviewed to gather patient's information.

RESULT

The median and inter-quartile range of patient delay, health service delay, diagnosis delay, initiation delay and total treatment delay in days were 30.0(76.00), 7.0(14.50), 3.0(4.00), 3.0(4.00) and 64.0(90.25) respectively. Furthermore, the prevalence and 95%CI of unacceptable delays; patient delay, health service delay, diagnosis delay, initiation delay and total treatment delay were 46.6%(39.3, 53.3), 45.5%(38.2, 52.8), 48.3%(41.0,55.6), 37.6%(30.5,44.8), 61.8% (54.7,68.9) respectively. In multiple logistic regression analysis, the significant factors associated with unacceptable patient delay were age (OR: 3.88;

95%CI: 1.35, 11.18; p= 0.012), distance from home to first health facilities attended (OR: 3.98; 95%CI: 1.56, 10.15; p= 0.004), attending the T/CM practitioners (OR: 10.51; 95%CI, 1.80, 55.39; p=0.006), attending the private practitioners (OR: 0.24, 95%CI: 0.09, 0.60; p= 0.002) and stigma (OR: 4.81; 95%CI: 1.59, 14.60; p=0.006). On the other hand, the significant factors associated with unacceptable health service delay were negative results of initial sputum smear (OR:14.48; 95%CI: 2.30, 91.34; p=0.004), number of visits to health facilities (OR: 4.99 95%CI: 2.76, 9.03; p= <0.001) and types of first health care facilities attended (OR: 5.78; 95%CI: 1.58, 21.11; p= 0.008)

CONCLUSION

This study showed that there was a substantial delay in case finding in Kelantan. Raising public awareness about symptoms of TB, curability and benefit of utilizing available governmental health facilities through health education campaign might shorten the patient delay. Health care personnel in both private and government sectors should be reminded on the important of early diagnosis and prompt treatment of TB. Traditional and complementary practitioners should be well-cooperated in contributing to Malaysian health care system by interacting with both private and governmental health sectors.

CHAPTER ONE

INTRODUCTION

1.1 TB Burden

1.1.1 Globally

It has been estimated that approximately one-third of the world's population is infected with *Mycobacterium tuberculosis.* More than eight million people developed active TB every year, and about 1.8 million die of the disease (Dye *et al.*, 1999).

The trend of TB is increasing globally. The total number of new TB cases and its incidence rate per capita increased at a rate of 1.8% and 0.4% per year between 1997 and 2000, respectively. In 2000 there were estimated 8.3 million or 137 per 100,000 populations of new TB cases globally. Of these 3.7 million (44%) or 61 per 100,000 populations were infectious pulmonary cases and 5.4 million (65%) were in adults aged 15 to 49 years. 11% of all new TB cases in adults occurred in persons infected with HIV (Corbett *et al.*, 2003). The 22 high burden countries (incidence rate more than 100, 000 populations) account for approximately 80% of the estimated number of new TB cases (all forms) arising worldwide each year. These countries are; India, China, Indonesia, Nigeria, Bangladesh, Pakistan, Ethiopia, South Africa, Philippines, Kenya, DR Congo, Russian federation, Vietnam, UR Tanzania, Brazil, Uganda, Thailand, Mozambique, Zimbabwe, Myanmar, Afghanistan, and Cambodia (WHO, 2005).

The WHO African Region (essentially sub-Saharan Africa) had the highest annual incidence (290 per 100 000 population), while the South-East Asian Region had the largest number of cases (3.0 million). Half of the new cases were in the top five countries, all in Asia and 15 highest incidence countries, 13 were in Africa. It is estimated that the prevalence was twice the incidence in 2000 (Corbett *et al.*, 2003). Schulzer *et al.* (1992) suggested that there would be a dramatic increase in the number of cases of TB due to HIV infection in sub-Saharan Africa.

TB is one of the ten leading causes of death worldwide (Murray and Lopez, 1997) and the second cause of death among communicable diseases (Frieden *et al.*, 2003). 1.84 million people died from TB in 2000, of which 12% was attributable to HIV and the proportion was much greater in the WHO African region. The death rates varied dramatically in high burden countries, from nine per 100,000 populations in Brazil to 139 per 100,000 populations in South Africa. The case fatality rates in these two countries were 13% and 27% respectively. TB was the cause of 11% of all adult AIDS deaths. (Corbett *et al.*, 2003). The death rates among HIV-positive patients are much higher during the time they are being treated for TB than patient without HIV (Raviglione *et al.*, 1997).

TB remains the public health problem not only in the developing countries but also in developed and industrialized countries. In Australia, Hong Kong, China, Japan, Malaysia and Singapore, the number of cases has not decreased for several years (WHO, 2002a).
The resurgence of TB has been not only attributed by HIV infection but also with the increasing poverty (Druker *et al.*, 1994), increasing immigration (Cantwell *et al.* 1994),

drug resistance (Frieden *et al.*, 1993), dismantling of control programs, and poor adherence to treatment (Brudney and Dobkin, 1991).

TB kills more people than any other single infectious agent and death from TB comprises 26% of all avoidable deaths in developing countries. More than 90% of global TB cases and death occur in the developing world, where 75% are in the most economically productive age group (15 – 54 years) (Ahlburg, 2000).

1.1.2 Burden of TB in Western Pacific Region

There are an estimated two million cases of all types of TB in the Western Pacific Region; of these about 850,000 are infectious smear positive cases. However, less than half of infectious cases are actually detected. This region is home to four of the 22 high burden countries in the world. These four countries are Cambodia, China, the Philippines and Vietnam which account for one quarter of the global TB burden. TB detection rate is low in this region which was at 41% of estimated incidence (WHO, 2002a).

The seven high TB burden countries in the region which account for 94% of TB prevalence in this region are Cambodia, China, the Lao People's Democratic Republic, Mongolia, Papua New Guinea, the Philippines and Vietnam. Nearly half of the cases in these countries are believed to be infectious, but the detection rate, at 44% is lower than the regional average of 45%. (WHO, 2002a). In 2003, among the countries mentioned only Mongolia and Vietnam reached the 70% case detection rate. (WHO, 2003a)

1.1.3 Burden of TB in Malaysia

Malaysia is one of the countries in the Western Pacific Region with intermediate burden of TB (incidence rate between 25 to 100 per 100, 000 population). This disease is still a great challenge for public health in this country. It is an important cause of mortality amongst the infectious disease. It showed an increased trend by 3.5 per 100,000 populations since 1990 to 2000. The incidence rate per 100,000 populations in 2002 for all TB type and infectious smear positive cases were 58.7 and 32.4, respectively (MOH 2000a; MOH 2002c).

With regard to Kelantan the incidence rate per 100, 000 populations for all type and infectious smear positive were 68.1 and 46.2, respectively in 2002, which also showed an increasing trend from 65.3 and 42.0, respectively in 2000 (MOH, 2000a). In 2000, the number of reported deaths due to TB was 942 out of 15, 057 giving a case fatality rate of 6.3%. In 2002, there was an increase in the number of reported deaths due to TB, giving a case fatality rate of 7.2 %. (MOH 2000a; MOH 2002c). The five highest smear positive PTB incidence districts in Kelantan for year 2002 were Tumpat, Bachok, Pasir Puteh, Kota Bharu and Tanah Merah. On the other hand, the five highest number of sputum smear positive PTB cases by districts in Kelantan were in Kota Bharu, Tumpat, Pasir Mas, Bachok and Pasir Puteh (Kelantan State Health Department, 2002).

1.2 Introduction to study area

Kelantan is one of the 13 states in Malaysia. It is located at northeast of Peninsular Malaysia in a land area of about 14,922-sq.km and 1,522, 200 population. Malay ethnicity is the majority, constitutes 94.1% of population followed by 4.6% Chinese, 0.5% Indian and 0.8% other ethnicities. The state is devided into ten administrative districts i.e Kota Bharu, Pasir Mas, Tumpat, Pasir Puteh, Bachock, Kuala Krai, Machang, Tanah Merah, Jeli and Gua Musang (Kelantan State Health department, 2003).

About 80.0% of the population live in the north of the state that covers 20% of total land area. Kota Bharu , the state capital is rapidly growing town being the focal point for Kelantan's administration and business activities (Kelantan State Health department, 2003).

There are ten district health offices, 59 health clinics, four maternity and child clinics, 203 community clinics and 62 dental clinics. In addition, there are 207 private clinics three private hospitals, 68 operating pharmacy and 30 private dental clinics in Kelantan. All the private hospitals are situated at Kota Bharu, the state capital city (Kelantan State Health department, 2003).

This study was conducted in four districts of Kelantan namely Kota Bharu, Tumpat, Bachok and Pasir Mas. All the other three districts surround the Kota Bharu district.

These four districts were situated at northern part of Kelantan together with Pasir Puteh, Machang and Tanah Merah. The four districts chosen in this study have the highest number of sputum smear positive PTB cases as mention earlier. Figure 1 shows the Kelantan Map highlighting the four districts under study (Kelantan State Health department, 2003).

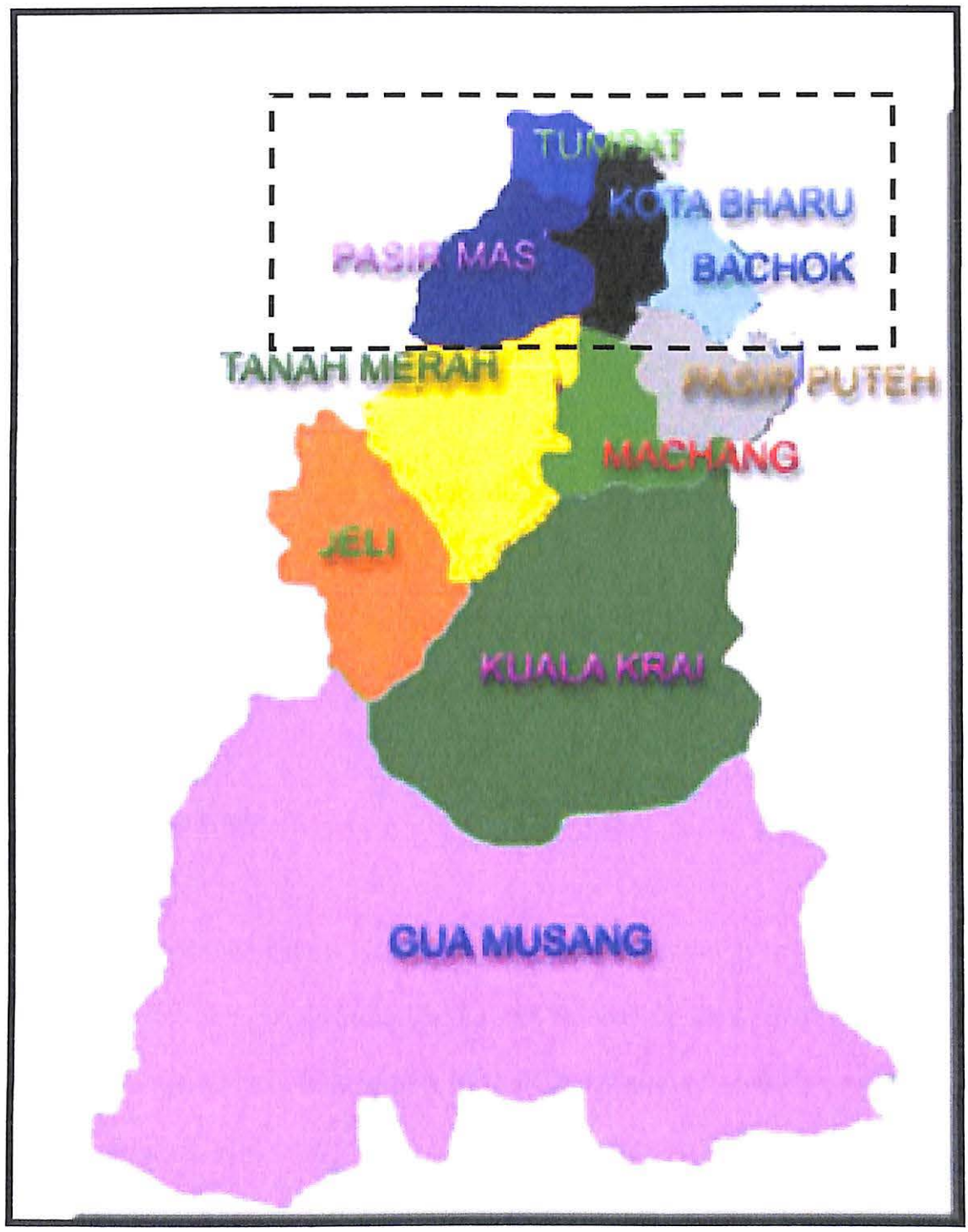

Figure 1: Kelantan state with ten administrative districts. The dot square is showing the four districts under study.

1.3 Justification of the study

In 1993, the World Healh Organization declared a state of global emergency for TB, due to steady increase of the disease worldwide (WHO, 1994). In Malaysia TB remains a major public health problem. Particular to Kelantan there is an increasing trend for all types of TB and smear positive PTB. Case finding is the important element of TB control so, it is imperative to explore more about the delay in starting treatment for TB.

There were only two local studies regarding delay treatment done. Both of them were conducted at town area and hospital based. One was done at Penang hospital (Hooi, 1994) and the other one was conducted at University Malaya Teaching hospital (Liam and Tang, 1997).

1.4 Rationale of the study

The main strategy of tuberculosis control in developing countries is to improve the cure rate by treating as early as possible the largest number of diagnosed TB cases, and subsequently to improve case finding; that is, to diagnose cases as quickly as possible and as many as possible (Kochi, 1991).

Delay in diagnosis is also the main factor for fatality in tuberculosis patients. It was reported in a Bolivian study that the cause of death of TB patients was due to delay in

diagnosis which contributed to 38.9% of the patients (Olle Goig, 2000). The main contributer to the tuberculosis fatalities after reviewing autopsy on TB death patients in Yugoslavian hospital is the late detection of tuberculosis (Ellis *et al.*, 1983).

The problem of delayed diagnosis of tuberculosis in patients with HIV infection has recently been emphasized. Forty-five percent of those whose diagnosis was delayed died of tuberculosis as compared with 19 percent of those who were diagnosed earlier. The cause of delayed diagnosis is not due to atypical presentations of tuberculosis but to error of manangement (Barnes, *et al.*, 1991).

Tuberculosis from ongoing transmission of *M. tuberculosis* will continue to develop unless patients are diagnosed early and contacts are more completely identified. Study done in Contra Costa country, California with the annual rate 12.5 cases/100 000 population found that 53% developed tuberculosis because of unidentified as contact, 27% developed tuberculosis because of delayed diagnosis of their sources, 18% associated with treatment of the contact and 1% delayed being elicited as contact (P.Chin *et al.*, 2000)

In view of this and limited information about the delayed treatment it is essential in conducting a study to determine the delay in treatment and the factors influencing on it. Despite a control programme launched in 1961, there was no single study done in east coast of Malaysia to assess the delay treatment of TB. Hence, conducting this study may provide the important information on the case finding, clinical management and control of TB in Malaysia.

CHAPTER TWO

CHAPTER TWO

OBJECTIVE, RESEARCH QUESTIONS AND HYPOTHESIS

2.1 General objective

1. To determine the prevalence of delays in TB treatment and factors influencing on it.

2.2 Specific objective

1. To determine the prevalence of patient delay, health service delay, diagnosis delay, treatment initiation delay and total treatment delay.

2. To identify the factors associated with the unacceptable patient delay and unacceptable health service delay.

2.3 Research questions.

1. What is the prevalence of various unacceptable delays (patient delay, health service delay, diagnosis delay, initiation delay and total treatment delay)?

2. Is there an association between unacceptable patient delay and socio demographic parameters, patient health conditions and patient's preferences?

3. Is there an association between unacceptable health service delay and socio demographic parameters, patient health conditions and health service factors?

2.4 Hyphothesis

1. There is an association between unacceptable patient delay and socio demographic parameters, patient health conditions and patient's preferences.

2. There is an association between unacceptable health service delay and socio-demographic parameters, patient's health conditions and health service factors.

2.5 Definitions of operational terms

1. Definition of operational terms about delays and the acceptable period for each of them were based on literatures and considering the local burden of TB and the health care system in this country. There are no national or internationally accepted standard regarding criteria upon which to define an 'acceptable' period for delay. In previous studies, panel of experts have agreed on an acceptable period for total treatment delay (duration from the onset of symptoms to the treatment commencement) of 30 days (Perkis *et al.*, 1996) or 60 days (Asch *et al.*, 1998). When the total treatment delay is broken into patient delay and health service delay, most studies agreed with 30 days as the 'acceptable' period for patient delay (Rajeswari *et al.*, 2002; Demissie *et al.*, 2002; Odusanya *et al.*, 2004) and 15 days for health service delay (Demissie *et al.*, 2002; Odusanya *et al.*, 2004). The acceptable period for diagnosis delay and initiation delay was defined as one week (Rajeswari *et al.*, 2002) and three days (Perkis *et al.*, 1996) respectively. However, in this study, in view of the implementation of National Tuberculosis Information System (TBIS) throughout Malaysia in 2003 (Kelantan State Health Department, 2003) and measurement of the health service delay started from the initial consultation at government health facilities researchers concluded to define the 'acceptable period' for health service delay as seven days (it was not six days because to take in consideration the working day in practical). Based on the definition mentioned above below are the definitions of the delays in detail determine for this study:

1.1. Patient delay

Duration from onset of symptoms to initial consultation at government health facilities.

1.2. Health service delay

Duration from initial consultation at government health facilities to commencement of treatment. This duration is the summation of diagnosis and initiation delay.

1.3. Diagnosis delay

Duration from initial consultation at government health facilities to smear positivity.

1.4. Initiation delay

Duration from smear positivity to commencement of treatment.

1.5. Total treatment delay

Duration from onset of symptoms to treatment commencement. This delay is the summation of patient delay and health service delay.

1.6. Unacceptable delay :

- Unacceptable patient delay : patient delay more than 30 days
- Unacceptable health service delay : health service delay more than seven days.
- Unacceptable diagnosis delay : diagnosis delay more than three days
- Unacceptable initiation delay : initiation delay more than three days
- Unacceptable total treatment delay : total treatment delay more than 37 days.

2. Sputum smear-positive pulmonary tuberculosis

a) Tuberculosis in a patient with at least two initial sputum smear examinations (direct smear microscopy) positive for acid fast bacilli (AFB)

b) Tuberculosis in a patient with one sputum smear examination positive for AFB and radiographic abnormalities consistent with active pulmonary TB as determined by treating doctor

c) Tuberculosis in a patient with at least one sputum smear examination positive for AFB and sputum culture positive for *M. tuberculosis*

(MOH, 2002a)

3. Government health facilities

Government health clinics or government hospitals including the teaching hospital, excluding the community clinics.

4. Symptoms

symptoms were defined as one or more of the following occuring in the previous two years and lasting two weeks or more axcept for haemoptysis, if present it was considered significant: cough, pleuritic chest pain, fever, loss of weight, loss of appetite, and night sweat before they attended the government health facilities for seeking treatment.

(Asch *et al.*, 1998)

5. Eligible Household contacts

Household members of an index patients who had been living in the same house as index patients for at least four weeks previously. (Klausner *et al*,. 1993)

6. Income

Monthly per capita income in Malaysian ringgit

7. Home distance to the first health facility attended

Distance in kilometers

8. HIV-infected case

Patients with reactive ELISA test for HIV-1 and HIV-2, confirmed by particle agglutination (PA) test.

9. Treatment centres one (TC1)

The TC1 were chest clinics and certain health clinics which were responsible for diagnosis, initiation and continuation of anti-TB treatment.

(MOH, 2002d)

10. Treatment centres two (TC2)

The 'TC2' was the term used for the centers which were responsible for the treatment continuation only. TC2 can be the health clinics, community clinics or chest clinics.

(MOH, 2002d)

11. Nearest health clinic :

A government health facility, which was located nearest to the respondent's living quartes, with distance measured in kilometers, and not in terms of difficulty of physical access.

12. Over-the-counter (OTC) drug

Available without a prescription. OTC drugs are available without a prescription, simply "over the counter." OTC drugs are in contrast to prescription drugs that require a doctor's order. (Anonymous)

13. Traditional medicine

Traditional medicine is the sum total knowledge, skills and practices on holistic healthcare, which is recognized and accepted by the community for its role in the maintenance of health and the treatment of diseases. Traditional medicine is based on theory, beliefs and experiences that are indigenous to different cultures, and that is developed and handed down from generation to generation.

(MOH, 2001)

14. Complementary medicine

Refer to wide range of health interventions originating from different cultures across thousands of years of history.

(MOH, 2001)

15. Covariate pattern

A single set of values for the covariates in a model.

(Hosmer and Lemeshow, 2000)

CHAPTER THREE

CHAPTER THREE

LITERATURE REVIEW

3.1 Bacteriology of TB

Mycobacterium tuberculosis, the causative agent of TB, usually is readily identified by its rough, non-pigmented, corded colonies on oleic-acid-albumin agars; a positive niacin test; generally weak catalase activity, which is lost completely by heating to 68^0 C; and a positive nitrate reduction test (American Thoracic Society, 1990).

Those mycobacterium that are obligate pathogens causing human disease (with the exception of *M. leprae*) are known as the '*M. tuberculosis* complex'. This consists of *M. tuberculosis*, which makes up the vast bulk of cases, *M. africanum* and *M. bovis*. *M. microti* and the bacillus Calmette-Guerin (BCG) vaccine strain, while strictly members of TB 'complex', only cause disease under special circumstances (Ormerod, 2003).

3.2 Pathogenesis of TB

M. tuberculosis enters the body via the respiratory tract through inhalation of respiratory droplet nuclei, which are very small in size (1-2μm or less). It reaches the alveoli within the lungs, where the organism replicates. The larger particle containing the numerous *M. tuberculosis* bacilli that can also be generated by the patients are efficiently excluded and does not reach alveoli by the physical barriers of nasopharynx and upper respiratory tract

(Riley *et al.*, 1995). The organisms grow slowly for two to 12 weeks, until they reach 10^3 to 10^4 in number which is sufficient to elicit a cellular immune response that can be detected by tuberculin skin test (Smith and Wiegneshaus, 1989). Once in the alveoli, the organisms are taken up by alveolar macrophages and spread throughout the body via hematogenous route (Dannenberg, 1994).

Once the organisms have made their way into the lung, they have four potential fates. *(1)* The initial host response can be completely effective and kill all bacilli; *(2)* the organism can begin to multiply and grow immediately after infection causing the primary TB; *(3)* bacilli may become dormant and never cause disease referred to as latent infection which can be detect by tuberculin skin test; *(4)* latent organisms can eventually begin to grow, with resultant clinical disease, known as reactivation TB (Dannenberg, 1994).

Granuloma is the cardinal feature of initial response to TB and its role in host defenses against *M. tuberculosis*. In persons with intact cell-mediated immunity, collections of activated T cells and macrophages from granulomas limit multiplication and spread of the organism (Saunder and Cooper, 2000). Individuals with latent TB infection but not active are not infectious and thus cannot transmit the organism. Flynn and Chan (2001) conclude that the host responses is important in controlling the latent infection which may include macrophages activation, maintenance of granuloma structure, CD4 T cells, CD8 T cells, IFN-γ, and TNF-α. Still to be tested are the contribution of other cytokines or chemokines to the establishment and control of latent TB infection.

3.3 Transmission of Mycobacterium tuberculosis

The *M. tuberculosis* is carried on airborne droplet nuclei which are produced when persons with PTB cough, sneeze, speak, or sing (American Thoracic Society, 1990). Airborne route which transmits TB was suspected by Koch in 1932 to proof tubercle bacilli as the cause of TB. Wells at the Harvard school of Public Health in 1934 made a major breakthrough in the understanding of airborne transmission of TB (Cited in Rieder, 1999).

Fennelly *et al.* (2004) presented a novel approach to directly assessing the potential infectiousness of patients with PTB. Cough aerosol sampling system was used to culture the cough-generated aerosol from 16 smear positive PTB patients. Among the subject only 33 % was found to be aerosol cultured positive, this suggested that there may be considerable variability in the ability to produce potentially infectious aerosols. The size distributions suggest that most of the viable particles in these cough-generated aerosols are immediately respirable. An editorial by Nardell commented on Fennelly study sampling occurs at extremely close proximity to the infectious source where there was little time for droplet nuclei to dry and it is unclear whether some of these cultured organisms remain infectious in a room very long (Nardell, 2004).

Patients in whom tubercle bacilli can be detected by direct examination of the sputum smear are the main sources of transmission (Shaw and Williams, 1954; Lienhardt, 2003). Smear positive persons expectorate $10^8 - 10^{10}$ bacilli daily (Potterger, 1948), or about $10^6 - 10^7$ per ml of sputum (Yeager *et al.*, 1967).

Study by Shaw and Williams (1954) also showed that not only cases of infection but also cases of TB disease, are more frequent among contact of sputum positive compare to the culture only positive and sputum negative cases. This finding is also similar with to Underwood *et al.* (2003) study between 1997 to 1999 in East London which found the rate of TB disease among contacts were 4.9% of those exposed to sputum positive cases compared to 1.9% of those exposed to smear-positive PTB and 0.9% of those exposed to non PTB cases.

The effect of chemotherapy has been shown to reduce the infectivity of TB. These facts seem to indicate the very rapid and powerful action by the drugs on infectivity. Brooks *et al.* (1973) for example studied 107 subjects living in close contact with 21 patients with positive sputum. After a period in hospital of up to 23 days, 19 of these patients, while still positive, were sent home (none of the 72 tuberculin-negative in contacts after the beginning of treatment showed conversion of their tuberculin tests).

Gunnels *et al.* (1974) studied contacts of 155 patients who were sent home after one month of treatment in hospital. These patients were divided into three groups according to whether they were negative on culture, positive on culture, or positive both on culture and on direct examination at the time of discharge from hospital. No difference was found in the frequency of infection in the contacts corresponding to these three groups of patients.

The effect of chemotherapy on the cough-generated aerosol culture for *M. tuberculosis* by Fennelly *et al.* (2004) showed that there were rapid decrease in cough-generated aerosol culture within the first three weeks of effective treatment of sputum-positive TB patients and the decrease rate to be considerably more rapid than the sputum culture and this suggested that patients became noninfectious within a few weeks of effective treatment.

The duration of infectiousness especially among the sputum positive TB is the crucial importance for the risk of infectivity. The risk of becoming exposed is greatly enhanced if infectiousness is prolonged compared with a short duration of infectiousness. An untreated case of infectious TB will remain infectious for longer period of time than a patients treated in timely manner (Rieder, 1999). The proportion of household contacts being infected were 23% from the time of diagnosis of TB made in index case suggest that probably the infection occurred one to two months prior to treatment of the index cases (Riley and Moddie, 1974). A Study by Reichler *et al.* (1996) in United State showed 32% of close contacts of active PTB were positive TST. A Study carried out by Klausner *et al.* (1993) from April 1989 through February 1990 in Kinshasa, Zaire found that there was high percentage of infectivity among household contacts, 60% whose exposed to HIV-seropositive sputum culture positive index cases and 63% whose exposed to HIV-seronegative sputum positive index cases at the time the patients being diagnosed

Several host factors influence transmission. Increasing age is shown to be the risk factors to have TB infection. Klausner *et al.* (1993) found the prevalence of *M. tuberculous* infection increased with increasing age of household contacts. A Study in

Gambia by Lienhardt *et al.* (2003) had similar finding with age and sex interaction by which the odds of having TST positive is higher in both sex with increasing age group but more in male.

3.4 Risk factors for disease given that infection has occurred.

In general, persons who are infected with *M. tuberculosis* have approximately a 10% risk for developing active TB during their lifetime. Information from the tuberculin-positive placebo group in BCG vaccination trials indicated that the incidence of TB is the highest in the first few years after infection and rapidly falls off (D'Arcy Hart and Sutherland, 1977). It is a strong factor, with recent infection being ten times more likely to produce a case than long standing infection (Rieder, 1999).

Horsburgh (2004) reviewed prospective cohort studies and published reports between 1949 to 2003 in United States to determine which patients had the greatest lifetime likelihood of reactivation disease. The risk of reactivation decrease for the first nine years after conversion and then 10% per decade thereafter. The annual risk of reactivation are greatest for patients with a skin-test induration > 15 mm and patients with known recent conversion. The lifetime risk of TB falls with increasing age at the time of first positive skin test. Children less than five years have the highest lifetime risk (10% to 12%) and adult more than 35 years exhibiting a lifetime risk of less than 5% (Horsburgh, 2004).

Many studies show that TB was affecting males compared to females (Haffernan *et al.*, 1975; Rieder *et al.*, 1989; Enarson, Wang and Dirks, 1989). In the United States males are twice as likely to have clinical TB and this finding was similar across the two races (White and Black). In the urban area in Canada, the TB incidence rates for those born in Canada were observed to be higher for men than for women. A striking difference in the likelihood of developing extra-PTB was found between male and female patients with TB in the study on extraPTB in the United States. All other extrapulmonary forms except pleural TB were consistently more likely to develop in female than male. Pleural TB was equally likely to develop in male and female (Rieder *et al.*, 1990).

The HIV-seropositive patients have an extraordinary high risk of developing clinical TB, compared to HIV-seronegative individuals. Selwyn *et al.* (1989) found that eight of 212 HIV-infected intravenous drug users developed TB in a two year period of observation, a case rate of 8/100 person-years of observation. Of these, seven developed within a subset of 49 persons who were known to be tuberculin-positive. Thus, the case rate for persons who were dually infected with both HIV and *M. tuberculosis* was 7.9/100 person-years. This exceeds the lifetime risk of a person with TB infection who is not HIV-infected.

A Cohort study by Cowie (1994) of 1,153 older gold miners with and without silicosis found that the relative risk for TB was 2.8 for men with silicosis compared with that in the men without silicosis. Conditions like diabetes mellitus haematologic malignancies and uraemia or therapies like cancer chemotherapy, that interfere with cell-mediated immunity also increase the risk of TB (Cited in Rieder, 1999).