SELECTED RISK FACTORS ASSOCIATED WITH TREATMENT FAILURE AMONG NEW SMEAR-POSITIVE PULMONARY TUBERCULOSIS PATIENTS FROM SEVEN PROVINCES IN THE LOWER SOUTHERN PART OF THAILAND

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**A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE
(EPIDEMIOLOGY)
FACULTY OF GRADUATES STUDIES
MAHIDOL UNIVERSITY
2013**

Thesis
entitled

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude and deep appreciation to Prof. Prasert Assantachai, my major-advisor, for his guidance, invaluable adviser, supervision and encouragement throughout the work of the thesis. He was never lacking of kindness and support. I would like to express my sincere thanks to my co-advisors, Assoc. Prof. Nitipatana Chierakul and Assoc. Prof. Weerasak Muangpaisan, for their helpful guidance and support with respect to the statistical analysis of data, as well as their constant kindness.

I am grateful to thank Mrs. Sirinapha Jittimanee, the Public Health Technical Officer Professional Level, Bureau of Tuberculosis, Department of Communicable Disease Control, Ministry of Public Health, my external examiner for her suggestion and support in defense of this thesis.

I am special thanks to the Office of Disease Prevention and Control 12 Songkhla, TB center 12 Yala, 7 Provincial Public Health Offices (consisted: Songkhla, Yala, Pattani, Narathiwat, Trang, Phatthalung and Saturn), 45 government hospitals, all staff of the tuberculosis clinic and also special unforgettable thanks those subjects for their cooperation in collecting data.

Finally, I wish to express my deepest gratitude to my family and my friends for their love, encouragement and support that inspired me to accomplish my study.

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ABSTRACT

This research was a case-control study designed to identify factors associated with treatment failure among new smear-positive pulmonary tuberculosis patients from seven provinces in the lower southern part of Thailand. One hundred and eighty-nine subjects who suffered from tuberculosis treatment failure were recruited as the case group. The same number of patients who were treated successfully were allocated to the control group. The data was collected from May 2012 to August 2012. Multiple logistic regression analysis was used to identify the risk factors of treatment failure.

The study results showed four factors significantly associated with treatment failure: 1) positive sputum smear after two or three months of treatment (positive 1^+, adjusted OR= 15.08, 95%CI= 4.84-47.00 and positive 2^+/ 3^+, adjusted OR=11.76, 95%CI =2.01-68.78), 2) having drug susceptibility testing done (adjusted OR= 9.45, 95%CI=4.03-22.1), 3) living in urban area (adjusted OR=2.44, 95%CI=1.05-5.67), and 4) having a family member as DOT observer (adjusted OR= 3.25, 95%CI=1.33-7.92).

With the increasing demand for tuberculosis control, successful initial is needed. Those who live in an urban area should receive the first priority to be closely monitored as well as supervised by health personnel during the DOT regimen. The presence of acid-fast bacilli in the sputum after a few months of treatment is another alarming factor that the health personnel involved must pay more attention to. Also, health personnel should put more effort in avoiding treatment failure.

KEY WORDS: PULMONARY TUBERCULOSIS / NEW SMEAR-POSITIVE / TREATMENT FAILURE

79 pages

ปัจจัยคัดสรรที่ทำให้ผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อมีผลการรักษาล้มเหลว ใน 7 จังหวัดภาคใต้ตอนล่างของประเทศไทย

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บทคัดย่อ

วิทยานิพนธ์ฉบับนี้เป็นการศึกษาแบบ case-control study เพื่อศึกษาปัจจัยที่ทำให้ผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อมีผลการรักษาล้มเหลว ใน 7 จังหวัดภาคใต้ตอนล่างของประเทศไทย โดยมีผู้ป่วยวัณโรคที่เคยมีผลการรักษาล้มเหลว จำนวน 189 ราย ถูกนำเข้ามาเป็นกลุ่ม case ในขณะที่ผู้ป่วยที่มีผลการรักษาหายในจำนวนที่เท่ากันถูกสุ่มเลือกเป็นกลุ่ม control ดำเนินการเก็บข้อมูลระหว่างพฤษภาคม 2555 - สิงหาคม 2555 โดยใช้ multiple logistic regression ในการวิเคราะห์ปัจจัยที่สัมพันธ์กับการมีผลการรักษาล้มเหลว

ผลการศึกษาพบว่ามี 4 ปัจจัยที่สัมพันธ์กับผลการรักษาล้มเหลวในผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อ คือการมีผลการตรวจเสมหะยังคงเป็นบวกในเดือนที่ 2 หรือ 3 ของการรักษา (positive 1+; adjusted OR= 15.08, 95% CI= 4.84 - 47.00 และ positive 2+/ 3+; adjusted OR= 11.76 (95% CI= 2.01-68.78) ผู้ป่วยที่ได้รับการทดสอบความไวของเชื้อต่อยารักษา (adjusted OR= 9.45; 95% CI= 4.03-22.14) ผู้ป่วยที่อาศัยอยู่ในเขตเมือง (adjusted OR= 2.44; 95% CI= 1.05-5.67) และผู้ป่วยที่ยินยอมให้ญาติเป็นพี่เลี้ยงในการกำกับการกินยา (adjusted OR= 3.25; 95% CI= 1.33-7.92)

การรักษาผู้ป่วยให้ประสบความสำเร็จเป็นสิ่งที่จำเป็นลำดับแรกในการควบคุมวัณโรค โดยเฉพาะผู้ป่วยที่อยู่ในเขตเมืองควรได้รับการกำกับการกินยาต่อหน้าอย่างใกล้ชิดจากเจ้าหน้าที่สาธารณสุข ในขณะเดียวกันผู้ป่วยที่มีผลเสมหะหลังการรักษาในเดือนที่ 2 หรือ 3 ยังคงเป็นบวก แสดงถึงสัญญาณเตือนให้ผู้ที่มีส่วนเกี่ยวข้องให้ความสนใจและเพิ่มความพยายามในการหลีกเลี่ยงการมีผลการรักษาล้มเหลว

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CHAPTER I
INTRODUCTION

1.1 Rationale and background

Tuberculosis was the seventh leading cause of death worldwide (1). World Health Organization (WHO) estimated new cases of tuberculosis up to 9.4 million cases in 2009, and the prevalence of the disease was estimated to be 14 million cases. Of these, 1.3 million death cases were not HIV-infected cases. In addition, 250,000 cases were estimated to be multi-drug resistant tuberculosis (MDR-TB) (2).

Thailand is one of the 22 high TB burden countries. The prevalence of the disease ranked the 14th of the world (2) and it was also the ninth leading cause of death of Thai people (3). In 2009, the prevalence and the incidence of TB in Thailand estimated by WHO were 130,000 cases and 93,000 cases, respectively. The mortality cases were also estimated to be 12,000 cases each year (2). The Bureau of Tuberculosis, Ministry of Public Health reported the number of registered TB patients with DOTS (Directly Observed Treatment, Short-course) in the year 2006-2008 were 58,339 cases, 56,124 and 63,430, respectively. The cure rate of new smear positive TB cases with DOTS were 70%, 77% and 76%, respectively, while treatment failure was 2 percent each year. The 12th Office of Disease Prevention and Control situated in Songkhla which covers seven provinces in the lower southern part of Thailand, namely, Trang, Phatthalung, Satun, Songkhla, Yala, Pattani and Narathiwat, reported the highest incidence of new smear positive TB patients. In 2006-2008, the cure rates were 61%, 75% and 77 %, respectively. However, the failure rate in new smear positive TB patients increased from 1 percent to 2 percent during the same period (4, 5).

DOTS is one of the six strategies recommended by WHO to stop tuberculosis. DOTS should be effectively implemented worldwide with good acceptance. Five components of DOTS strategy are as follows:

1) Any government and related executive persons must place the high priority on TB control.

2) The patients with suspicious symptoms must be screened by sputum examination in order to find the new cases. The incidence must also be reported.

3) The positive sputum smear cases must complete DOTS for 6 months.

4) The antiTB drugs must be tested to achieve good quality and without shortage.

5) Standard case recording and reporting system must be implemented in order to follow and evaluate the treatment situation in each patient (2, 6).

WHO sets the target of 90% success rate for TB treatment by the year 2015 (7). During the past two decades (1995-2009), 49 million cases received DOTS worldwide and 41 million cases were cured (8). The success rate of DOTS increased every year. With the latest report published by WHO in the year 2008, the success rate of DOTS was 87 percent. On the other hand, treatment failure was 2 percent each year (2). Although the incidence of TB seems to decline, the emergence of multidrug-resistant tuberculosis (MDR-TB) increases in an alarming pattern. In MDR-TB cases, the process of getting the culture and sensitivity results requires a longer period of time and more expenditure. Moreover, the mortality rate would be higher in HIV-infected cases (8).

The studies of treatment failure among new smear-positive cases caused by MDR-TB had been published as follows:

1. The study conducted by WHO in six countries regarding the impact of MDR-TB in DOTS. In Peru and Hong Kong where DOTS had been used in all new cases, those who had MDR-TB would be more likely to suffer from treatment failure compared to those whose the AFB were susceptible to all antiTB drugs. Although the MDR-TB cases were excluded from the analysis, the risk of treatment failure was still greater among those whose AFB resist to rifampicin and isoniazid. The authors recommended the rapid diagnosis and effective treatment for the MDR-TB cases in order to reduce the spreading of MDR-TB organism in the community. Since the first-line drug regiment was not effective in such cases (9).

2. The study in Egypt (10) reported the results of treatment failure would lead to the spreading of AFB in the community and might be the leading cause of emergence of MDR-TB organisms, absenteeism and loss of work force. Two factors significantly related to treatment failure were lack of knowledge of TB treatment and

diabetes mellitus. Therefore, tight control of blood glucose level and closed supervision by others were recommended for diabetic patients who also suffered from TB.

3. The study in Yunnan, China (11) reported the failure of DOTS if health volunteers in the community were used in this program. In addition, the presence of AFB after two months of treatment would be the significant factor leading to treatment failure. The health personnel in TB clinic should know their patients individually in order to achieve successful treatment.

Treatment failure in new TB cases with DOTS program is defined by the presence of AFB during the 5^{th} to 6^{th} month of treatment (12). Apart from the spreading of AFB in the community, more expenditure is certainly required to solve these cases. Following the unit cost analysis, the average cost of treatment in MDR-TB cases was 92,884.40 baht. However, the average cost of TB re-treatment for general expenditure, chest x-ray, sputum examination and antiTB drugs were 1069.89, 153.74, 157.37 and 180.84 baht, respectively (13). The results of this study also agreed with the study in Malaysia (14). The impacts of the first treatment failure involve medical, public health and socioeconomic issues. For the individual patients, they had to follow the longer period of treatment and were subjected to increase chance of treatment failure due to drug-resistant TB organisms (15, 16).

Since the 12^{th} Office of Disease Prevention and Control situated in Songkhla reported the highest incidence of TB in Thailand, and there is no study involving treatment failure among new cases in Thailand in the past. This study was, therefore, designed to explore the risk factors of treatment failure among new cases of TB. The identified risk factors would be vital to create the treatment guideline for the country to control TB in the area.

1.2 Research question

What are the associated factors of treatment failure among new smear-positive pulmonary TB patients living in seven provinces of the lower southern part of Thailand?

1.3 General objective

To study the associated factors of treatment failure among new smear-positive pulmonary TB patients living in seven provinces of the lower southern part of Thailand.

1.4 Specific objectives

1. To analyze the host factors of the new smear-positive pulmonary TB patients with treatment failure living in seven provinces of the lower southern part of Thailand.
2. To analyze the agent factors of the new smear-positive pulmonary TB patients with treatment failure living in seven provinces of the lower southern part of Thailand.
3. To analyze the environmental factors of the new smear-positive pulmonary TB patients with treatment failure living in seven provinces of the lower southern part of Thailand.

1.5 Research hypothesis

1. Host factors associated with treatment failure among new smear-positive pulmonary TB patients living in seven provinces of the lower southern part of Thailand.

2. Agent factors associated with treatment failure among new smear-positive pulmonary TB patients living in seven provinces of the lower southern part of Thailand.

3. Environment factors associated with treatment failure among new smear-positive pulmonary TB patients living in seven provinces of the southern part of Thailand.

1.6 Scope of the study

Population in this study were new smear positive pulmonary TB patients who were treated with DOTS strategy during October 2004–September 2010 at the public hospitals and the 12th TB center situated in Yala which also supervised TB control in seven provinces (Songkhla, Yala, Pattani, Narathiwat, Trang, Phatthalung and Satun) of the lower southern part, Thailand. Data was collected during May 2012-August 2012.

1.7 Definition of terms

DOTS (Directly Observed Treatment, Short-course) means the strategy controlling TB under supervision of other persons during the intake of antiTB drugs. Six-month treatment regimen is required especially the initial two months.

Drug susceptibility testing (DST) is defined as the testing of a strain of Mycobacterium tuberculosis for its susceptibility or resistance to one or more anti-TB drugs.

First-line drug refers to the standard anti-TB drugs used for any new case of TB, namely, isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin.

New smear-positive pulmonary TB patient means any new patient who was diagnosed of pulmonary TB by the physician and has positive sputum smear results for acid fast bacilli (AFB positive) and was also registered to the hospital.

Initial phase means the first intensive 2-3 months of DOTS treatment using the first-line drugs.

Treatment outcome was classified into 6 categories as follows.

(1) **Cure** means the conversion of smear-positive AFB status into smear-negative AFB status at the end of treatment regimen.

(2) **Treatment completed** means the conversion of smear-positive AFB status into smear-negative AFB status during the course of treatment, but the result of sputum smear test at the end of treatment regimen is not available.

(3) **Treatment failure** means the persistence of smear-positive AFB at the 5^{th} month of treatment or at the end of treatment regimen.

(4) **Default** means the patients whose treatment were interrupted for at least 2 consecutive months.

(5) **Dead** means the patients who die for any reason during the course of treatment.

(6) **Transfer out** means the patients who are transferred to the other hospitals whose treatment outcome is unknown.

Treatment success means the combination of cure and treatment completed as mentioned above (17).

Rural area means the area under the supervision of the Sub-district Administrative Organization.

Urban area means the area under the supervision of municipal authority.

1.8 Expected outcomes and benefits of the study

1) The results of the study could be applied by the other health care personnel to control TB and sequentially to decrease treatment failure in the new smear positive pulmonary TB patients.

2) The interventions using our study results can decrease the spreading of TB in the community and also reduce the re-treatment which is much more difficult.

CHAPTER II
LITERATURE REVIEW

This study aims to identify factors associated with treatment failure among new smear-positive pulmonary TB patients living in seven provinces in the lower southern part of Thailand. Literature review was done in the category as follows:

2.1 Knowledge about TB

2.2 The previous research

2.3 Conceptual framework

2.1 Knowledge about TB

2.1.1 Causes

Mycobacterium tuberculosis is the cause of tuberculosis (TB) in human (18). There are four species within the genus Mycobacterium, namely, M. tuberculosis, M. africanum, M. bovis and M. microti. Ninety-nine percent of patients infected by Mycobacterium are from M. tuberculosis (19). These aerobic bacteria grows more slowly than other bacteria (20).

2.1.2 Symptoms

The symptoms of TB are similar to the other lung diseases, such as lung cancer, chronic obstructive lung disease, etc.

2.1.2.1 Fever and night sweating: The patients develop low-graded fever in the evening due to the increasing number of M. tuberculosis in the afternoon. The inflammatory process goes on slowly. If M. tuberculosis spreads to bronchia or the other organs, patients develop high fever and chill which can occur in any period of time (21).

2.1.2.2 Weight loss: Seventy percent of the patients suffer from loss of appetite and weight loss (21).

2.1.2.3 Chronic cough: Coughing is the important symptom of TB as a result of inflammatory process in respiratory system. The patients will have dry cough initially and then productive cough with sputum, either purulent or bloody, and eventually chronic cough. Chronic cough usually persists more than 3 weeks (21).

2.1.2.4 Hemoptysis: Although the occurrence of hemoptysis is quite rare, the presence of hemoptysis usually reflects tuberculosis. The pathogenesis of hemoptysis shows the involvement of artery aneurysm (Rasmussen's aneurysms) in the lung. As a result, the arteries in the lung cavity stop working (21, 22).

2.1.2.5 Dyspnea: Dyspnea is also rare in TB patients. The patients develop dyspnea if there is a large cavity within the lung or during acute infection.

2.1.2.6 Thoracic pain: Thoracic pain is usually caused by pleuritic pain when the inflammatory process involves the pleura. It is usually found during the early stage of infection and pleuritic pain will disappear after a few weeks of treatment (21).

2.1.2.7 Hoarseness of voice: This symptom is caused by the persistent and severe chronic cough (21).

2.1.3 Transmission of TB

Approximately 95 percent of the route of entry of Mycobacterium is via the respiratory tract. The droplet nuclei, smaller than 5 microns, produced by the cough of infected patients will spread in the air and survive for several hours. When the susceptible people with weakened immunity breathe these droplet nuclei containing TB organisms into their lungs; M. tuberculosis will grow in the lung tissue. Then, these infected cases can further transmit the TB organisms to the other people (23, 24).

The patients with lung cavity are more likely to spread the disease due to the higher number of organisms in the cavity lesion. In addition, the route of entry could be via the skin and digestive tract (19).

2.1.4 Diagnosis

2.1.4.1 History taking and physical examination

The general symptoms are weakness, weight loss, low grade fever in the afternoon or evening, chest pain, fatigue and night sweating. Irregular menstruation is also found in women. The purulent sputum is often yellow or green in color and fetid. Crepitation sounds can be detected in the lungs. In severe cases, the bulging of chest wall can be found due to TB empyema. Some patients may have symptoms associated with other pathological organs. Doctors may detect the inflammation of the urinary tract, lymph nodes and the other parts of the body, especially in HIV-infected patients. If the patient has a high fever, severe headache, vomiting and confusion, TB meningitis should be suspected due to its high mortality. Sometimes the patients may have symptoms of cardiac tamponade and congestive heart failure which are also shown in radiographic findings. Ascites is also detected in TB peritoneum. Hoarseness of voice is found in TB larynx. A history of contact with TB patients must also be asked during history taking (25).

2.1.4.2 Specimen examination

The discharge or tissue from the body of the suspected patients can be kept in two types. The first one is for the sterile specimens which is free from contamination of other bacteria, such as cerebrospinal fluid, pleural effusion etc. The second one is for the contaminated specimens such as sputum, stool etc. In addition, the collected specimens can be classified by body systems as follows (26):

(a) Sputum specimens from the respiratory tract are the most common specimen in daily practice. Health personnel should advise the patient to collect sputum after waking up in the morning for 3 consecutive days. 95% of pulmonary TB can be detected by this type of specimen examination.

(b) Specimen from the gastrointestinal tract can be collected either by stool or gastric washing. The unconscious patients or children are the good candidates for this type of specimen examination. One to two grams of stool specimen should be kept in one container.

(c) Specimen from the urinary tract can be collected as 15 ml. of urine in the morning at least 3-5 times during a period of time. Sterile technique must be used during specimen collection.

(d) Specimen from the skin should be collected in a large amount as much as possible.

(e) The other fluid specimen, such as pleural effusion, peritoneal fluid, synovial fluid and pericardial fluid, should be collected at least 15 ml. For blood culture, 5 – 20 ml. of blood should be kept in a sterile container.

2.1.4.3 The laboratory diagnostics

(a) The staining technique. The unique feature of acid fastness of TB organism is employed during the staining process by using fuchsin and auramine stain. The liquid specimen must be concentrated by centrifuge technique before staining. The solid or concentrated specimens can be stained directly. For sputum examination, at least 5,000-10,000 organisms per milliliters are required for the specimen to be detected by these techniques. The three popular staining methods are Ziehl-Neelsen (hot stain), Kinyoun (cold stain) and fluorochrome, where fluorescence stain and fluorescence microscope are used. The results can be reported as negative, 1^+, 2^+ and 3^+ depending on the number of M. tuberculosis in the specimen.

(b) TB culture. This is the standard technique to verify the presence of M. tuberculosis and is also used for drug susceptibility tests for the treatment benefit. Specimens of all types can undergo TB culture. The results can be reported as 5 categories, namely, negative, 1^+, 2^+, 3^+ and 4^+. The occurrence of colony must be tested again to verify as M. tuberculosis by special staining in order to reveal the serpentine cord pattern and using the other biochemical tests such as niacin test (26, 27). TB culture should be done in the suspected patients who are negative for AFB staining, those who are resistant to anti-TB drug and HIV-infected cases (28).

(c) Drug susceptibility testing (DST). There are 2 methods of drug susceptibility testing. The first method is the direct method where the sputum or specimen are placed in two types of media, the one contains antiTB drug tested while the other contains placebo. Large amount of the organisms in the specimen is needed. This is a disadvantage of the test. The second method is the indirect method, where the organisms in the specimen are left in the media for at least 3-4 weeks to grow completely. The advantage of this test is its better quality control and the disadvantage is it needs longer duration of the test. However, with the new technique of molecular biology, polymerase chain reaction (PCR) can be used to get the rapid results within

24 - 48 hours. The disadvantage of this new technique is the higher cost and it must be done by trained technicians (26, 27).

2.1.4.4 Radiography

Since pulmonary TB is the most common site of TB infection, chest radiography is, therefore, a necessary test in the suspected patients. Chest radiography has high sensitivity but low specificity. So, sputum examination should be done to support the diagnosis. However, some findings of the chest radiography may be characteristic to TB, e.g., a cavity lesion (25).

2.1.4.5 Tuberculin skin test

Tuberculin is an extract of M. tuberculosis which was first produced by Robert Koch in 1891. Purified protein derivatives (PPD), derived from the cell wall of M. tuberculosis, is a popular tuberculin used at present. Tuberculin skin test is a very useful tool in various aspects, e.g., epidemiologic study, monitoring the disease progression, screening for the infected case and making the differential diagnosis in the suspected cases whose sputum results or chest radiography are negative. Mantoux test, a favorite test of tuberculin skin test, is done by injecting 0.1 ml. of purified protein derivatives (PPD) into the inner surface of the forearm, approximately 2 – 3 inches from the cubital fossa. The skin reaction is then assessed between 48 and 72 hours after administration. A five - millimeter or more induration around the injected site indicates the active process of TB infection. In a severe reaction, vesicles or blebs can be seen (25, 29, 30).

2.1.4.6 The other tests

(a) Rapid culture. The result of this test can be reported within 7-10 days. However, the cost of laboratory instrument used and the expenditure are quite expensive. A trained technician is also required to do the test.

(b) Antigen detection method. This test is ideal for CSF (cerebrospinal fluid) where M.tuberculosis is homogeneous found in the fluid.

(c) Polymerase Chain Reaction (PCR). This is a very high sensitive test since it can detect at least 3 cells of M. tuberculosis in a specimen within 48 hours.

(d) Biochemical detection of specific component of M. tuberculosis. Some examples of this kind of test are tuberculosteric acid and mycolic acid.

(e) Enzyme linked immunosorbent assay (ELISA). Immunoglobulin antibody will be specifically targeted by purified antigen specific to M. tuberculosis.

(f) DNA fingerprint: RELP (Restriction fragment length polymorphism). This method is used in case of an outbreak to identify the site of spreading in various locations, such as in a prison, hospital etc. (25).

2.1.5 Classification of pulmonary TB patients

Smear-positive case

(a) Those whose sputum smear examinations by direct smear method are positive at least 2 times.

(b) Those whose sputum smear examinations by direct smear method are positive at least 1 time plus a chest radiographic finding characteristic of pulmonary TB.

(d) Those whose sputum smear examinations by direct smear method are positive at least 1 time plus a positive culture result.

Smear-negative case

(a) Those with chest radiographic finding characteristic of pulmonary TB and 3 negative sputum examinations. The patients are treated by antiTB drugs prescribed by the physicians.

(b) Those with 3 negative sputum examinations by direct smear method and a positive culture result.

2.1.6 The registration of pulmonary TB

There are six types of registration as follows;

(1) “New” means any patient who has been treated for pulmonary TB or treated less than 1 month.

(2) "Relapse" means any pulmonary TB patient who had been cured but the disease recurs later with a positive result of either sputum examination or culture method.

(3) "Transfer in" means any registered TB patient who is referred to another hospital.

(4) "Failure" refers to any pulmonary TB patients with positive sputum examination at the 5th month of treatment or those who have negative sputum examination at the beginning of treatment but the sputum examination turns to be positive at the second month of treatment.

(5) "Treatment after default" refers to any patient who returns to receive treatment again after stopping treatment for 2 consecutive months.

(6) "Other cases" refer to any patient who is not fit into the above categories (25).

The subjects in this study were all had positive sputum examinations plus being registered as "New" cases.

2.1.7 Directly Observed Treatment, Short-course (DOTS)

Directly Observed Treatment, Short-course (DOTS) regimen is one of the five strategies that WHO has recommended to control TB worldwide. To achieve this goal, five strategies must be implemented as follows:

1. The government or health authority must give the tuberculosis control at the high priority level.

2. Any suspected case must be screened by sputum examination and registered.

3. The positive sputum smear patients must be treated by DOTS for 6 months, especially during the first two months.

4. Only quality drugs must be used without any shortage.

5. The standard recording and reporting system must be set up to monitor progression in individual patient (2, 6).

DOT (Directly Observed Treatment) was originally designed to increase drug compliance. DOT observers can be nurse, public health care worker, public

health volunteer or even family member. They should be assessed as reliable person to do the job and appropriate for any individual patient (31).

In 1997, DOTS was firstly introduced into Thailand (31) with the objectives of reducing TB spreading, effective treatment without relapse and MDR-TB prevention (24). DOTS treatment is divided into 2 phases. The initial 2 months of intensive period can convert the state of sputum smear from positive to negative smear up to 80 percent (32). Newly smear-positive pulmonary TB patients will be treated by first-line drug regimen including 2EHRZ(S)/4HR (2 = 2months of initial phase, 4 = 4 months of continuous phase, E = Ethambutol, H = Isoniazid, R = Rifampicin, Z = Pyrazinamide, and S = Streptomycin) (32). Currently, two or more active drugs can be combined into a single tablet or fixed-dose combination (FDC) such as Rifinah (H and R), Myrin-P (E, H, R, Z, and S) etc. (24).

The recommended dosage of each drug for TB treatment based on body weight of patient (kilogram) is shown as follows (31).

E (Ethambutol) = 25 mg/ kg/ day

H (Isoniazid) = 10 mg/ kg/ day (≤ 300 mg/ kg)

R (Rifampicin) = 10 mg/ kg/ day (≤ 600 mg/ kg)

Z (Pyrazinamide) = 35 mg/ kg/ day (≤ 2,000 mg/ kg)

S (Streptomycin) = 15 mg/ kg/ day

Precaution: Ethambutol should not be used in children aged lower than 6 years old because the children cannot the side-effect of color blindness. Streptomycin should not be used in pregnant women. Streptomycin should not be used more than 750 milligrams per day in the elderly (31).

Table 2.1 Recommended dosage of each antiTB drug based on body weight (31).

Drug	**Daily dose (mg)**		
	30-39 kg	**40-49 kg**	**≥ 50 kg**
E	600-800	1000-1200	≥1200
H	300	300	300
R	300	450	600
Z	1000	1500	2000
S	500	750	1000

2.1.8 Schedule of sputum examination to monitor treatment

The newly positive sputum smear pulmonary TB patients treated by first-line drugs must undergo 2 tests of sputum examination at the end of the second month of treatment in order to assess the state of sputum conversion which reflects the effective spreading control of TB organisms. Meanwhile, 2 tests of sputum examination at the end of the fifth month of treatment must be done in order to assess the failure of treatment and at the end of drug regimen in order to determine the state of complete cure (33).

2.1.9 Treatment outcomes

Treatment outcome was classified into 6 categories as follows.

(1) **Cure** means the conversion of smear-positive AFB status into smear-negative AFB status at the end of treatment regimen.

(2) **Treatment completed** means the conversion of smear-positive AFB status into smear-negative AFB status during the course of treatment, but the result of sputum smear test at the end of treatment regimen is not available.

(3) **Treatment failure** means the persistence of smear-positive AFB at the 5th month of treatment or at the end of treatment regimen.

(4) **Default** means the patients whose treatment were interrupted for at least 2 consecutive months.

(5) **Dead** means the patients who die for any reason during the course of treatment.

(6) **Transfer out** means the patients who are transferred to the other hospitals whose treatment outcome is unknown.

Treatment success means the combination of cure and treatment completed as mentioned above (17, 34).

2.1.10 Drug resistance

According to the 3rd survey of drug-resistant TB in Thailand (2005–2006), 1.65 percent of new TB patients were infected by MDR-TB, while it was 34.54 percent of re-treatment patients were caused by MDR-TB. The corresponding numbers from the 2nd survey (2001-2002) were 0.69% and 14.24%, respectively (35). The

spreading of MDR-TB organisms in the community will create many significant problems. Firstly, it would be more difficult to treat and decreases the chance of complete cure. Secondly, the cost of re-treatment is much more expensive. Thirdly, the patients will suffer more from taking many antiTB drugs for a longer period of time. Sequentially, great adverse outcomes regarding the medical, public health and socio-economic aspects will be followed (15, 16). Drug resistance can be divided into 2 categories as follows;

2.1.10.1 The classification by history of treatment

(a) Primary drug resistance or initial drug resistance refers to drug resistance of M. tuberculosis in patients who never receive anti-TB drug.

(b) Acquired drug resistance refers to drug resistance of M. tuberculosis in patients who have received antiTB drugs more than 1 month (36).

2.1.10.2 The classification by type of drug resistance

(a) Mono-drug resistance means any anti-TB drug resistance of M. tuberculosis in the standard first-line drug regimen.

(b) Poly-drug resistance means two or more anti-TB drug resistance of M. tuberculosis in the standard first-line drug regimen excluding multi-drug resistant TB (isoniazid and rifampicin) (37).

(c) Multi-drug resistance (MDR) means isoniazid and rifampicin resistance of M. tuberculosis and the organisms may also resist to another anti-TB drug in the first-line drug regimen (8).

(d) Extensively drug-resistance (XDR) means MDR-TB patients whose the causative TB organism also resist to fluoroquinolone and the injectable antiTB drugs in the second-line drug regimen (amikacin, kanamycin or capreomycin) (8).

The newly smear-positive pulmonary TB patients who are at high risk of drug resistance are those who also have HIV infection, diabetes mellitus, a big lung cavity, prisoner, history of contact with MDR-TB patients and treatment failure outcome. DST with 4 - 5 antiTB drugs (H, R, S, E, Z) must be done in all these cases. The combination of the first-line and the second-line drug regimen must be used for 18 months (16, 35).

2.1.11 Tuberculosis prevention

2.1.11.1 BCG vaccine

WHO recommends BCG vaccine for the prevention of severe TB in children, such as TB meningitis (31, 38). The vaccine was firstly produced by Albert Calmette and Calmille Guerin. It was named after both of them 0.1 ml. for adults and 0.05 ml. for newborn are recommended to be given intradermal on the deltoid muscle region by a skilled nurse (29).

2.1.11.2 Chemoprophylaxis or preventive therapy

1) For those who live in the same household of the infected cases, especially children aged under 5 years old, isoniazid 5 mg/kg/day for 3 months must be given. Then, tuberculin skin test must be done. If a positive reaction occurs, the continuation of isoniazid for another 6 months must be done. If a negative reaction occurs, the patients can stop treatment and must receive BCG vaccination.

2) For HIV-infected cases with positive reaction to tuberculin skin test, isoniazid 5 mg/kg/day (≤ 300 mg/day) for 6-12 months must be given (31).

2.2 Previous research review

Previous studies regarding factor associated with treatment failure among newly smear-positive pulmonary TB patients are reviewed as follows;

Gender: The study done in West Bengal, India (39) and the study in Egypt (10) found no association between gender and treatment failure.

Age: The study done in West Bengal, India (39) and the study in Egypt (10) found an non-significant association between age and treatment failure. However, the study in China (41) found that TB patients aged 15-39 years old were more likely to achieve treatment success significantly more than those aged more than 65 years old (adjusted OR, 3.36; 95%CI, 2.47-4.56, p-value =0.001).

Education: The study in Brazil (40) found that poorly educated TB patients were more likely to suffer from treatment failure higher than those who were well-educated with the odds ratio of 2.84 (adjusted OR = 2.84, 95% CI = 1.20-6.70, p-value= 0.0175). However, the study in Egypt (10) found that poorly educated TB patients were more likely to suffer from treatment failure without statistical significance.

Occupation: The study in Egypt (10) found that unemployed TB patients associated with treatment failure (OR, 1.20; 95%CI, 0.63-2.30) without statistical significance.

Income: Hua Jianzhao et al. (11) reported that high income TB patients were likely to have lower rate of treatment failure with statistical significance (adjusted OR, 0.22; 95%CI,0.06-0.82, P=0.05). Meanwhile, the study by Ratraprakorn Phuanggernmak (42) found no association between financial status and treatment failure.

Marital status: The study in Egypt (10) found no association between marital status and treatment failure (divorce/ separated: OR 1.62; 95%CI, 0.63-4.24, single: OR 1.44; 95%CI, 0.77-2.70).

Residence: The study in West Bengal, India (39) found no association between living setting (urban and rural) and treatment failure. Meanwhile, the study in Taiwan (43) found the higher incidence of TB in the high mountain area in each region of the country (central: RR 15.0; 95%CI, 13.4-16.9, eastern: RR 14.7; 95%CI, 13.6-16.0, northern: RR 10.9; 95%CI, 9.9-12.0 and southern: RR 8.4; 95%CI, 7.8-9.1). Interestingly, the more distance people live from the mountain area, the less likely people will catch TB. Since this study would be conducted in 7 provinces in the lower southern part of Thailand. The geographic characteristics are quite similar to Taiwan, where the Gulf of Thailand will be on the east of the study area and Andaman Sea will be on the west. In addition, Nakhonsithammarat mountainrange locates in the central area of lower southern part of Thailand stretching from north to south and Sankalakhiri mountain range is the border between Thailand and Malaysia. Most of

our subjects lived in the plain area between mountains and the seacoast (44). Thus, this geographic factor was also included in this research.

Distance between home and clinic: The study in Egypt (10) found that TB patients whose home were 10 km. far from the clinic were more likely to have treatment failure without statistical significance (adjusted OR, 1.07; 95% CI = 0.97-1.18).

Alcohol drinking: The study in Brazil (40) found that TB patients who drank alcohol associated with treatment failure with statistical significance (adjusted OR = 2.78, 95%CI = 1.07-7.18, p-value = 0.035).

Smoking: The study in the Northeastern part of Brazil (45) found that smoking TB patients and were cure would be 2.34 times more likely to suffer from re-treatment (adjusted OR = 2.34, 95% CI = 1.17-4.68, p-value= 0.016). Accordingly, the study in China (46) found that smoking increased the risk of TB with the odds ratio of 1.93 (adjusted OR = 1.93, 95% CI = 1.49-2.49). This finding was also reported by another study done in South Korea (47).

Exercise: The study in the northwestern part of England (48) found that exercise was a non-significant preventive factor of TB (OR = 0.71, 95% CI = 0.44-1.12, p-value > 0.05).

Concomitant disease: The study in Egypt (10) found that 77.5% of new TB patients with diabetes mellitus had treatment failure (adjusted OR, 9.32; 95% CI, 2.7-31.69; p-value < 0.05). Again, the study in Indonesia (49) found that 22.2% of TB patients with diabetes mellitus still had positive culture at the end of treatment. Ratraprakorn Phuanggernmak (42) reported no association between diabetes mellitus and other concomitant diseases with treatment failure.

Treatment delay: The study in Brazil (40) found that 60-day or more treatment delay of TB patients associated with treatment failure (adjusted OR = 4.44, 95% CI = 1.30-15.15, p-value = 0.017). The study in West Bengal, India, found non-

significant association between 3-week or more treatment delay and treatment failure (39). Hua Jianzhao, et al. (11) also reported non-significant association between 30-day or more treatment delay and treatment failure (adjusted OR, 6.3; 95% CI, 1.3-32.0, p-value = 0.25).

Sputum smear status before treatment: The study in West Bengal, India, (39) reported non-significant association between 3+ positive sputum smear and treatment failure. However, Hua Jianzhao, et al. (11) found a significant association between 2^+ positive sputum smear and treatment failure (adjusted OR, 2.7; 95%CI, 1.0-7.1, p-value =0.05).

Sputum smear result after a few months of treatment: Hua Jianzhao, et al (11) found that the persistence of positive sputum smear after a few months of treatment significantly associated with treatment failure (adjusted OR, 6.0; 95%CI, 2.3-15.9, p-value < 0.001).

Cavity lung lesion: The study in China (41) found that TB patients with cavity lung lesions significantly associated with treatment failure (adjusted OR, 0.51; 95% CI, 0.39-0.65, p-value = 0.001).

Drug resistance: Marcos A, et al. (9) studied the impact of drug resistance among new TB cases who received short-course chemotherapy in 6 countries. It was found that treatment failure was significantly found in a higher degree among drug-resistant cases than in susceptible cases (RR, 5.35; 95% CI, 3.87-7.40). When multidrug-resistant TB cases were excluded from analysis, the patients were still 3.27 times more likely to end up with treatment failure (RR, 3.27; 95% CI, 2.20-4.87).

- MDR-TB cases (resistance to isoniazid and rifampicin) were 15.4 times more likely to have treatment failure (RR, 15.4; 95% CI, 10.6-22.4; p value < 0.001).
- Rifampicin-resistant cases excluding MDR-TB were 5.48 times more likely to have treatment failure (RR, 5.48; 95% CI, 3.04-9.07).
- Isoniazid-resistant cases excluding MDR-TB were 3.06 times more likely to have treatment failure (RR, 3.06; 95%CI, 1.85-5.05).

- Rifampicin-resistant cases were 5.47 times more likely to have treatment failure (RR, 5.47; 95%CI, 2.68-11.2).
- Isoniazid-resistant cases were 2.21 times more likely to have treatment failure (RR, 2.21; 95%CI, 1.00-4.51).
- Streptomycin-resistant cases were 2.33 times more likely to have treatment failure without statistical significance (RR, 2.33; 95%CI, 0.95-5.71).

DOT observer: Siripanichgon K et al (50) revealed that the patients whose DOT observers were their own relatives had more unsuccessful treatments than those whose DOT observers were health personnel (OR, 2.33; 95%CI, 1.17-4.62). Pima W. (51) also reported the same finding when compared to health personnel working in the prisons with the odds ratio of 3.1 but without statistical significance (crude OR = 3.1; 95%CI = 0.70-14.3).

Knowledge about TB: The study in Egypt (10) found that the patients who did not have knowledge about TB associated with treatment failure (adjusted OR, 4.87; 95%CI, 1.89-12.52; p-value < 0.05).

Attitude toward DOTS regimen: Ratraprakorn Phuanggernmak (42) found no association between attitude toward DOTS regimen and treatment failure.

However, due to the 6-year retrospective study was designed; some patients might have been died or transferred to other places, especially those who were HIV-infected or MDR-TB cases (52, 53). Some factors might have not been recorded and it was impossible to pursue and do more interviews with all these patients. Thus, knowledge about TB and attitude toward TB were not included in this study.

2.3 Conceptual framework

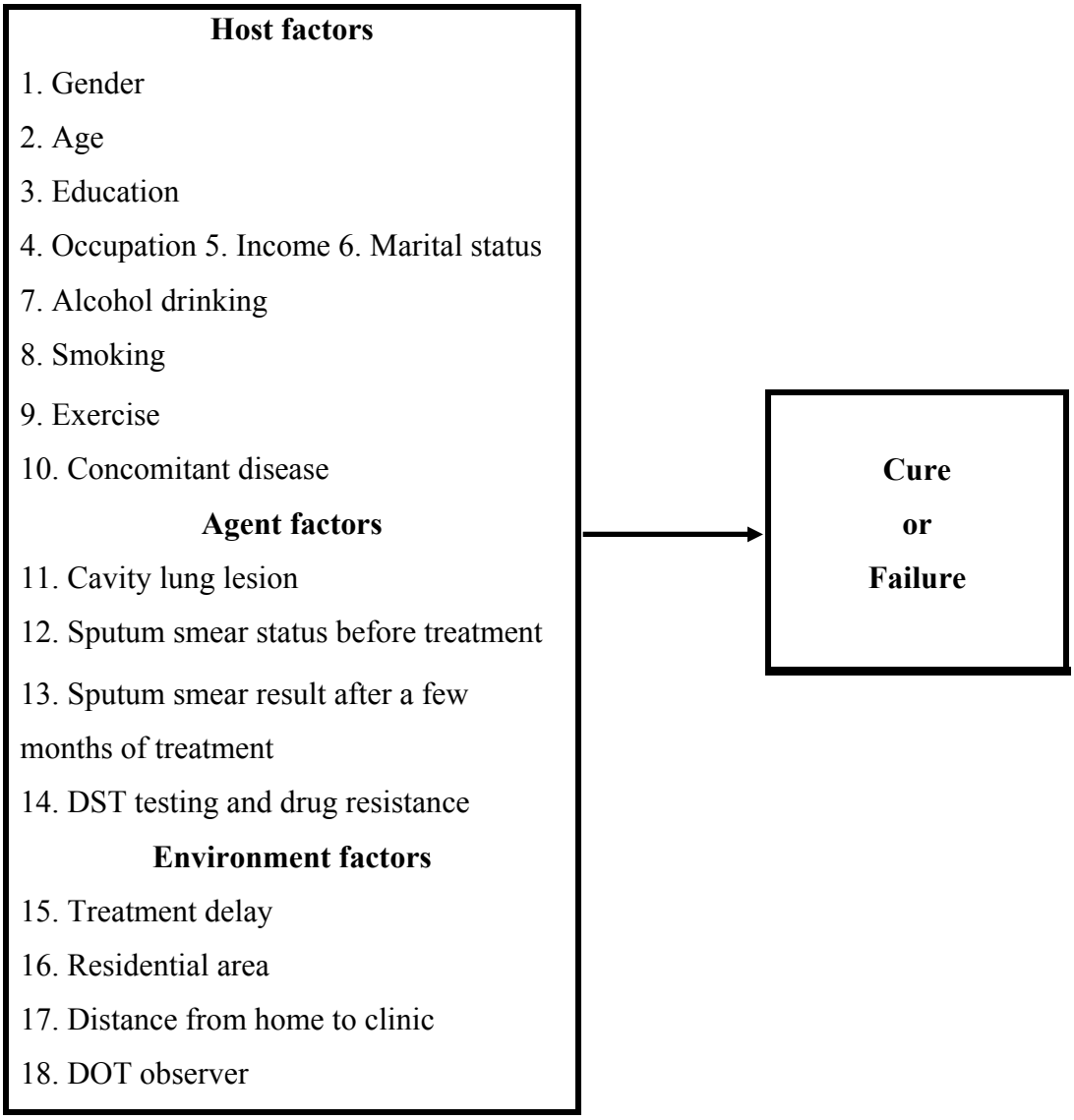

Figure 2.1 Conceptual framework

CHAPTER III
RESEARCH METHODOLOGY

3.1 Study design

This hospital-based unmatched case-control study was designed to determine factors associated with treatment failure among new smear-positive pulmonary TB patients. A ratio of case per control was 1:1.

3.2 Target population

New smear-positive pulmonary TB patients who were treated with DOTS regimen during October 2004–September 2010 at The 12th TB center Yala and the local public hospitals situated in seven provinces (Songkhla, Yala, Pattani, Narathiwat, Trang, Phatthalung and Satun) of the lower southern part of Thailand were recruited.

3.3 Definition of case and control

The sample population in this study was classified into 2 groups as follows;

Case group refer to new smear-positive pulmonary TB patients who were treated with DOTS regimen and had positive sputum smear result at the 5th or 6th month of treatment. These patients were labeled as treatment failure group.

Control group refer to new smear-positive pulmonary TB patients who were treated with DOTS regimen and had negative sputum smear result at least once during treatment and at the end of treatment (6th month). These patients were labeled as treatment cure group.

Inclusion criteria

1. New smear-positive pulmonary TB patients treated with DOTS regimen during October 2004–September 2010 at the 12th TB center Yala and the local public hospitals.

2. Living in seven provinces in the lower southern part of Thailand (Songkhla, Yala, Pattani, Narathiwat, Trang, Phatthalung and Satun).

3. Patients who had treatment outcomes with DOTS as either failure or cure.

4. Thai people aged more than 18 years old.

Exclusion criteria

1. Patients who were unable to provide required information and declined to participate in the data collection process.

3.4 Sample size estimation

The estimated sample size was calculated by using the quoted formula of Schlesselman JJ with the unmatched case-control ratio of 1:1 as follows (54).

$$n_1 = n_2 = \frac{\left[z_{\alpha/2}\sqrt{(1+1/k)p(1-p)}+z_{\beta}\sqrt{p_1(1-p_1)+\{p_2(1-p_2)/k\}}\right]^2}{(p_1-p_2)^2}$$

Where $p_1 = \frac{(OR)p_2}{(OR)p_2+(1-p_2)}$ and $p = \frac{(p_1+kp_2)}{(1+k)}$

And n_1 = sample size in case group, n_2 = sample size in control group

p_1 = proportion of risk factor in case group

p_2 = proportion of risk factor in control group

p = the average proportion of risk factor in the both group

OR = Odds Ratio, k = case group is as size as control group = 1

$Z_{\alpha/2}$ = 1.96 at α = 0.05 (two sided test)

Z_{β} = 1.28 at β = 0.10

Based on the evidence-based information from the study in Egypt (10), the distance from home to clinic more than 10 kilometers of new TB patients associated with treatment failure with the odds ratio of 2.74. Therefore, this odds ratio was used to calculate sample size. The odds ratio and proportion of distance from home to clinic more than 10 kilometers among new TB patients who had treatment cure (OR = 2.74 times and p_2 = 0.21) were used for calculation as follows,

$$p_1 = \frac{(2.74)0.21}{(2.74)0.21+(1-0.21)} = 0.42$$

$$p = \frac{(0.42+0.21)}{(1+1)} = 0.31$$

$$n_1 = n_2 = \frac{\left[1.96\sqrt{(1+1/1)0.31(1-0.31)}+1.28\sqrt{0.42(1-0.42)+\{0.21(1-0.21)/1\}}\right]^2}{(0.42-0.21)^2}$$

$$n_1 = n_2 = 100.21$$

Although the calculated sample size was 101 subjects, it would be inadequate for multiple logistic regression analysis as one independent variable in the model will relate to 10 outcomes or subjects (55). Thus, based on 18 independent variables in this study, at least 180 subjects would be needed for each group. At the same time, the incidence of new smear positive pulmonary TB was just 2% per year and 7-year retrospective study was originally designed, the sample size was, therefore, 100 % increased for each group, i.e., 202 subjects for each group.

3.5 Sample selection

3.5.1 Case group. All subjects over the past 7 years were purposively sampling.

3.5.2 Control group. The subjects recruited were those were treated in the same hospital at the same time (± 3 months) as in case group. If there were more than 1 candidate in the control group, simple random method would be used to select the subjects.

3.6 Research instrument

Case record form used in this study consisted of 2 parts as follows;

3.6.1 Data record form

Age, gender, marital status, concomitant disease, cavity lung lesions, sputum smear status before treatment, sputum smear result after 2-3 months of treatment, DOT observer, drug susceptibility testing and drug resistance were retrieved from the original Tuberculosis Treatment Card or TB 01 and Tuberculosis Registry or TB 03 and recorded in this data record form.

3.6.2 Structured questionnaire

Socio-demographic characteristics, namely, education, occupation, income, alcohol drinking, smoking, exercise, residential area and distance from home to clinic were retrieved by interview.

3.7 Validity instrument

Content validity and appropriateness of language used in case record form were inspected and modified by the major supervisor and the co-supervisors.

3.8 Data collection

Data were collected by the researcher and the health personnel working in the TB clinic. The objectives and process of data collection were discussed together by all members of the team. The following steps of data collection were as follows;

3.8.1 The research proposal was submitted to the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, for approval. It was approved in March 2012. In addition, the research approval was also acquired from the local public hospitals, e.g., Had Yai Hospital, Trang Hospital, etc.

3.8.2 The formal letters regarding the research, as part of a master degree thesis, issued by the Faculty of Graduate Studies, Mahidol University were sent to the director of the 12th TB center Yala, the Provincial Public Health Office in Songkhla, Yala, Pattani, Narathiwat, Trang, Phatthalung and Satun to ask for permission and cooperation in data collection process.

3.8.3 After the permission, the researcher contacted local health personnel working in TB clinic of each hospital for participation.

3.8.4 In TB clinic, researcher or local health personnel introduced themselves to the subjects who attended the clinic on that day. The subjects were informed about the research objectives and human right protection. The informed consent must be read and signed by the subjects.

3.8.5 For subjects who could not attend the TB clinic, the researcher or local health personnel would make a phone call to them to ask for verbal consent. Again, the subjects were informed about the research objectives and human right protection. After the verbal consent was approved by the subjects, data collection process would proceed further.

3.8.6 The relevant data were retrieved from the original Tuberculosis Treatment Card or TB 01 and Tuberculosis Registry or TB 03 and recorded in the data record form.

3.8.7 Structured questionnaire was also used during direct interview or phone interview until completed.

3.8.9 All data were checked for correctness before statistical analysis.

3.9 Data analysis

3.9.1 The data was analyzed by using PASW statistics 18 (copyright of Mahidol University, serial number: 5082368).

3.9.2 Statistical analysis

3.9.2.1 Descriptive statistics

Categorical variables, namely, gender, education, marital status, occupation, alcohol drinking, smoking, exercise, concomitant disease, residence, cavity lung lesions, sputum smear result before treatment, sputum smear result after 2-3 months of treatment, drug susceptibility testing, and drug resistance were described as frequency and percentage.

Continuous variables, namely, age, income, distance from home to clinic were described as median, and interquartile range (IQR).

3.9.2.2 Inferential statistics

Univariate analysis was performed to identify risk factors that associated with treatment failure. The strength of association was described as crude OR (crude odds ratio), 95% CI (95% confidence interval) and the statistical significance level ≤ 0.05. For one or more of the four expected cell frequencies in 2X2 table less than 5, Fisher's exact test would be used to identify association.

All the significant variables from univariate analysis that did not have multicollinearity relationship would be used for multiple logistic regression analysis_enter method (56, 57). The adjusted OR (adjusted odds ratio), 95% CI (95% confidence interval) and the statistical significance level ≤ 0.05 was acquired by the analysis.

CHAPTER IV
RESULTS

Since the public hospitals in 7 provinces in the lower southern part of Thailand (Songkhla, Yala, Pattani, Narathiwat, Trang, Phatthalung and Satun) were involved in the study including the 12th TB Center Yala, 45 public hospitals were finally recruited.

4.1 General characteristics of the subjects

Three hundred and seventy eight subjects were finally recruited. One hundred and eighty nine cases were allocated in the case group and similarly in the control group. The distribution of subjects in the province of Songkhla, Yala, Pattani, Narathiwat, Trang, Phatthalung and Satun were 43.90%, 14.8%, 13.8%, 9.5%, 7.4%, 6.3% and 4.2% respectively (Table 4.1). The distribution of subjects in the each public hospital was also shown in Table 4.2. The hospital names were listed in order according to the number of subjects. Table 4.3 showed the distribution of subjects in each year of TB treatment. The majority of subjects were recruited in the year 2008 (24.9% of the case group and 24.9% of the control group), year 2009 (20.6% of the case group and 21.7% of the control group), and year 2007 (15.3% of the case group and 15.3% of the control group).

Table 4.1 Distribution of the overall subjects classified by province

Provinces	Case group		Control group	
	number	percent	number	percent
Songkhla	83	43.9	83	43.9
Yala	28	14.8	28	14.8
Pattani	26	13.8	26	13.8
Narathiwat	18	9.5	18	9.5
Trang	14	7.4	14	7.4
Phatthalung	12	6.3	12	6.3
Saturn	8	4.2	8	4.2

Table 4.2 Distribution of the overall subjects classified by hospital

Province	Hospital	Case group		Control group	
		Number	Percent	Number	Percent
Songkhla	Songkhla	46	55.4	46	55.4
	Hat yai	13	15.7	13	15.7
	Sathing phra	5	6.0	5	6.0
	Sadao	5	6.0	5	6.0
	Khuan niang	4	4.8	4	4.8
	Rattaphom	4	4.8	4	4.8
	The pha	3	3.6	3	3.6
	Na mom	2	2.4	2	2.4
	Na thawi	1	1.2	1	1.2
	Total	83	100.0	83	100.0
Yala	TB center 12 Yala	10	35.7	10	35.7
	Yala	6	21.4	6	21.4
	Bannang sata	3	10.7	3	10.7
	Betong	3	10.7	3	10.7
	Yaha crown's prince	3	10.7	3	10.7
	Raman	3	10.7	3	10.7
	Total	28	100.0	28	100.0
Pattani	Pattani	6	23.1	6	23.1
	Yarang	3	11.5	3	11.5
	Yaring	3	11.5	3	11.5
	Nong chik	3	11.5	3	11.5
	Mayo	2	7.7	2	7.7
	Mae lan	2	7.7	2	7.7
	Khok pho	2	7.7	2	7.7
	Panara	2	7.7	2	7.7
	Kapho	1	3.8	1	3.8
	Thung yang daeng	1	3.8	1	3.8
	Sai buri crown's prince	1	3.8	1	3.8
	Total	26	100.0	26	100.0
Phatthalung	Khuan khanon	5	42.0	5	42.0
	Tamot	3	25.0	3	25.0
	Phatthalung	3	25.0	3	25.0
	Bang kaeo	1	8.3	1	8.3
	Total	12	100.0	12	100.0

Table 4.2 Distribution of the overall subjects classified by hospital (cont.)

Province	Hospital	Case group		Control group	
		Number	Percent	Number	Percent
Narathiwat	Narathiwasratchanakarin	3	16.7	3	16.7
	Sungai padi	3	16.7	3	16.7
	Tak bai	2	11.1	2	11.1
	Bacho	2	11.1	2	11.1
	Rangae	2	11.1	2	11.1
	Sukhirin	2	11.1	2	11.1
	Sungai kolok	2	11.1	2	11.1
	Choairong	1	5.6	1	5.6
	Ruso	1	5.6	1	5.6
	Total	18	100.0	18	100.0
Trang	Kantang	6	43.0	6	43.0
	Trang	6	43.0	6	43.0
	Na yong	2	14.0	2	14.0
	Total	14	100.0	14	100.0
Saturn	Saturn	5	62.5	5	62.5
	Tha phae	1	12.5	1	12.5
	Thung wa	1	12.5	1	12.5
	Langu	1	12.5	1	12.5
	Total	8	100.0	8	100.0
	Grand total	189	100.0	189	100.0

Table 4.3 Distribution of subjects classified by year of treatment

Year of treatment	Case group		Control group	
	Number	Percent	Number	Percent
2010	15	7.9	13	6.9
2009	39	20.6	41	21.7
2008	47	24.9	47	24.9
2007	29	15.3	29	15.3
2006	21	11.1	21	11.1
2005	27	14.3	27	14.3
2004	11	5.8	11	5.8
Total	189	100.0	189	100.0

The general characteristics of the case group

More than half of the subjects were male (75.7%). The number of subjects in the age group of 32-54 years old, more than 54 years old and less than 32 years old were 47.6 %, 27.5% and 24.9%, respectively. (median = 45 years; IQR = 11 years). The majority of subjects were educated in formal school and married.

The number of subjects classified by type of occupation were employee (36%), unemployed (29.6%) and agriculture (21.7%). The majority of the subjects had income per month as 5,000-8,000 THB 32.3%, less than 5,000 THB 20.6% and more than 8,000 THB 13.2%. (median = 7,000 THB; IQR = 3,000 THB). Nearly all subjects (81.5%) did not drink alcohol during treatment. Of the 189 cases in the case group, 140 cases (74.1%) did not smoke tobacco during treatment. Among the smoking subjects, 63.3% smoked occasionally. Regarding the exercise of the subjects, 85.7% did not regularly exercise. Furthermore, sixty-three subjects (33.3%) had concomitant diseases. The majority of the diseases were AIDS 15.9%, diabetes mellitus 11.6% and hypertension 4.2%. One hundred and forty cases (74.1%) had cavity lung lesions.

Sputum smear results before treatment were found in the category of 3+ positive 41.3%, 1+ positive 37.0% and 2+ positive 21.7%. The number of subjects who had sputum smear results after 2-3 months of treatment as 1+ positive and 2+ to 3+ positive 32.8% and 11.1%, respectively. Drug susceptibility test was performed in 100 subjects (52.9%). The prevalence of resistance to rifampicin, isoniazid, ethambutol, pyrazinamide and streptomycin were 26.0%, 22.0%, 13.0%, 7.0% and 6.0%, respectively. More than 20% of the tests were not available, especially for streptomycin (55%).

One hundred subjects (52.9%) of this group did not seek treatment until 16 – 50 days after the onset of symptoms. 23.8% and 23.3% of the subjects had duration of treatment delay of 50 days and less than 16 days, respectively (median = 32 days; IQR = 34.5).

Regarding the environmental factors, 59.3% lived in rural area, 79.4% lived on the mainland far from the coast. 56.1% had distance from home to clinic 4 - 14 kilometers (median = 8 kilometers; IQR = 11 kilometers). 78% of the subjects traveled to TB clinic by a private car. 14.8% and 13.8% traveled by a hired motorcycle and by a taxi, respectively. 93.6% of the subjects could travel to TB clinic without any

difficulty. Regarding DOT observer, 57.1%, 32.3% and 10.6% were local public health officer, relatives and health volunteer, respectively. (Table 4.4-4.6)

The general characteristics of the control group

More than half of the subjects were male (73.5%). The number of subjects in the age group of 32-54 years old, more than 54 years old and less than 32 years old were 54.0 %, 24.3% and 21.7%, respectively (median = 42 years; IQR = 22 years). The majority of subjects were educated in formal school and married.

The number of subjects classified by type of occupation were employee (39%), agriculture (31.2%) and unemployed (13.8%). The majority of the subjects had income per month as 5,000-8,000 THB 43.9%, more than 8,000 THB 22.2% and less than 5,000 THB 19.6% (median = 7,000 THB; IQR = 3,250 THB). Nearly all subjects (77.2%) did not drink alcohol during treatment. Of the 189 cases in the control group, 156 cases (82.5%) did not smoke tobacco during treatment. Among the smoking subjects, 57.6% smoked occasionally. Regarding the exercise of the subjects, 77.2% did not regularly exercise. Furthermore, forty-seven subjects (24.9%) had concomitant diseases. The majority of the diseases were AIDS 11.6%, diabetes mellitus 10.1% and hypertension 7.9%. One hundred and eighteen cases (62.4%) had cavity lung lesions.

Sputum smear results before treatment were found in the category of 1+ positive 43.4%, 3+ positive 31.7%, and 2+ positive 24.9%. The number of subjects who had sputum smear results after 2-3 months of treatment as 1+ positive and 2+ to 3+ positive 3.7% and 1.1%, respectively. Drug susceptibility test was performed in 29 subjects (15.3%). The prevalence of resistance to isoniazid, ethambutol and streptomycin were 3.4%. More than 20% of the tests were not available, especially for streptomycin (58.6%). One hundred and one subjects (54.4%) of this group did not seek treatment until 16 – 50 days after the onset of symptoms. 24.3% and 22.2% of the subjects had duration of treatment delay of 50 days and less than 16 days, respectively (median = 31 days; IQR = 32.5).

Regarding the environmental factors, 69.3% lived in rural area, 77.8% lived on the mainland far from the coast. 57.1% had distance from home to clinic 4 - 14 kilometers (median = 8 kilometers; IQR = 9.5 kilometers). 83.1% of the subjects traveled to TB clinic by a private car. 8.5% and 12.2% traveled by a hired

motorcycle and by a taxi, respectively. 95.7% of the subjects could travel to TB clinic without any difficulty. Regarding DOT observer, 64.0%, 27.0% and 9.0% were local public health officer, relatives and health volunteer, respectively. (Table 4.4-4.6)

Table 4.4 General characteristics of both case and control group

Characteristics	**Case group**		**Control group**	
	Number	**Percent**	**Number**	**Percent**
Gender				
Male	143	75.7	139	73.5
Female	46	24.3	50	26.5
Age (years) Median(IQR)	43(54-32)			
Median(IQR)	45(56.0-45.0)		42(54.0-32.0)	
< 32	47	24.9	46	24.3
32-54	90	47.6	102	54
> 54	52	27.5	41	21.7
Education				
No formal education	31	16.4	14	7.4
Educated	158	83.6	175	92.6
Occupation				
Unemployed	56	29.6	26	13.8
Agriculture	41	21.7	59	31.2
Employee	68	36	75	39.7
Vendor	11	5.8	14	7.4
Government Official/housewife	13	6.9	15	7.9
Income(Thai Bath= THB/month) Median(IQR)	7,000(8,000-5,000)			
Median(IQR)	7,000(8,000-5,000)		7,000(9,000-5,750)	
< 5,000	39	20.6	37	19.6
5,000-8,000	61	32.3	83	43.9
> 8,000	25	13.2	42	22.2
Missing 91 cases	64	33.9	27	14.3
Marital status				
Married	129	68.3	142	75.1
Single	49	25.9	41	21.7
Divorce/separated	11	5.8	6	3.2

Table 4.4 General characteristics of both case and control group (cont.)

Characteristics	Case group		Control group	
	Number	Percent	Number	Percent
Alcohol drinking	154	81.5	146	77.2
No	35	18.5	43	22.8
Yes				
Beer				
No	165	87.3	161	85.2
Yes	24	12.7	28	14.8
Wine				
No	187	98.9	188	99.5
Yes	2	1.1	1	0.5
Whisky				
No	187	98.9	186	98.4
Yes	2	1.1	3	1.6
Rice whisky				
No	174	92.1	176	93.1
Yes	15	7.9	13	6.9
Local brewed whisky				
No	186	98.4	187	98.9
Yes	3	1.6	2	1.1
Frequency of drinking alcohol *				
Occasional	22	62.9	33	76.7
Frequent	13	37.1	10	23.3
Drinking amount /time				
< 150-300 cc	6	17.2	7	16.3
150-300 cc	18	51.4	16	37.2
> 150-300 cc	11	31.4	20	46.5
Smoking during treatment				
No	140	74.1	156	82.5
Yes	49	25.9	33	17.5
Smoking habit *				
Occasionally	31	63.3	19	57.6
Every day	18	36.7	14	42.4
Exercise				
No	162	85.7	146	77.2
Yes	27	14.3	43	22.8

Table 4.5 Clinical characteristics of both case and control group

Characteristics	Case group		Control group	
	Number	Percent	Number	Percent
Concomitant disease				
No	112	59.3	131	69.3
Yes	63	33.3	47	24.9
Unknown/no exam	14	7.4	11	5.8
Hypertension				
No	150	79.4	151	79.9
Yes	8	4.2	15	7.9
Unknown/no exam	31	16.4	23	12.2
DM				
No	136	72	139	73.5
Yes	22	11.6	19	10.1
Unknown/no exam	31	16.4	31	16.4
AIDS				
No	137	72.5	151	79.9
Yes	30	15.9	22	11.6
Unknown/no exam	22	11.6	16	8.5
Heart disease				
No	133	70.4	135	71.4
Yes	4	2.1	3	1.6
Unknown/no exam	52	27.5	51	27
Liver disease				
No	140	74.1	134	70.9
Yes	2	1.1	2	1.1
Unknown/no exam	47	24.9	53	28
Kidney disease				
No	133	70.4	129	68.3
Yes	2	1.1	1	0.5
Unknown/no exam	54	28.6	59	31.2
Herpes zoster				
No	64	33.9	54	28.6
Yes	8	4.2	3	1.6
Unknown/no exam	117	61.9	132	69.8

Table 4.5 Clinical characteristics of both case and control group (cont.)

Characteristics	Case group		Control group	
	Number	Percent	Number	Percent
Cavity lung lesion				
No	49	25.9	71	37.6
Yes	140	74.1	118	62.4
Sputum smear status before treatment				
Positive 1+	70	37	82	43.4
Positive 2+	41	21.7	47	24.9
Positive 3+	78	41.3	60	31.7
Sputum smear result after 2-3 months of treatment				
Negative	99	54.4	180	95.2
Positive 1+	62	32.8	7	3.7
Positive 2+ and /3+	21	11.1	2	1.1
No test available	7	3.7	0	0
Drug susceptibility testing				
No	89	47.1	160	84.7
Yes	100	52.9	29	15.3
Isoniazid test*				
Susceptible	59	59	26	89.7
Resistant	22	22	1	3.4
Unknown	19	19	2	6.9
Rifampicin test *				
Susceptible	54	54	27	93.1
Resistant	26	26	0	0
Unknown	20	20	2	6.9
Pyrazinamide test*				
Susceptible	62	62	20	69
Resistant	7	7	0	0
Unknown	31	31	9	31
Ethambutol test *				
Susceptible	60	60	21	72.4
Resistant	13	13	1	3.4
Unknown	27	27	7	24.1
Streptomycin test *				
Susceptible	39	39	11	37.9
Resistant	6	6	1	3.4
Unknown	55	55	17	58.6

** calculated the specific group*

Table 4.6 Environmental characteristics of both case and control group

Characteristics	Case group		Control group	
	Number	Percent	Number	Percent
Treatment delay (days) Median(IQR)	32(49.3-16.0)			
Median(IQR)	32(49.5-15.0)		31(49.0-16.5)	
< 16	44	23.3	42	22.2
16-50	100	52.9	101	54.4
> 50	45	23.8	46	24.3
Residence				
Urban	77	40.7	58	30.7
Rural	112	59.3	131	69.3
Living environment relative to the sea coast				
Living in the mainland	150	79.4	147	77.8
Living near Andaman sea	7	3.7	6	3.2
Living near Gulf of Thailand	32	16.9	36	19
Distance from home to clinic Median(IQR)	8(14.0-4.0)			
Median(IQR)	8(15.0-4.0)		8(13.5-4.0)	
< 4 km.	34	18.0	37	19.6
4-14 km.	106	56.1	108	57.1
> 14 km.	49	25.9	44	23.3
Type of traveling to TB clinic				
Hired motorcycle				
Yes	28	14.8	16	8.5
No	161	85.2	173	91.5
Taxi				
Yes	26	13.8	23	12.2
No	163	86.2	166	87.8
Private vehicle				
Yes	148	78.3	157	83.1
No	41	21.7	32	16.9
Walk/bicycle				
Yes	1	0.5	3	1.6
No	188	99.5	186	98.4
Travel convenience				
very convenient	176	93.6	180	95.7
inconvenient	12	6.4	8	4.3
DOT observer				
Relatives	61	32.3	51	27
Health volunteer	20	10.6	17	9
Public health officer	108	57.1	121	64

4.2 Univariate analysis

Following the univariate analysis, the significant factors associated with treatment failure were shown as follows: no formal education (crude OR = 2.45, 95% CI = 1.26-4.78, *p-value* = 0.008), unemployed (crude OR = 2.49, 95% CI = 1.04-5.97, *p-value* = 0.042), smoking (crude OR = 1.66, 95% CI = 1.01-2.72, *p- value* = 0.047), no exercise during treatment (crude OR=1.77, 95% CI = 1.04-3.00, *p-value* = 0.04), having cavity lung lesions (crude OR = 1.72, 95% CI = 1.11-2.67, *p-value* = 0.016), positive sputum smear after 2-3 months of treatment [positive 1^+ (crude OR = 16.1, 95% CI = 7.10-36.53, *p-value* = 0.001) and positive 2^+ - 3^+ (crude OR = 19.09, 95% CI = 4.38-83.11, *p-value* = 0.001)], having drug susceptibility testing done (crude OR = 6.2; 95% CI = 3.81-10.10, *p-value* = 0.001), resistance to isoniazid (crude OR = 9.70, 95% CI = 3.81-10.10, *p-value* = 0.001), resistance to rifampicin (*p-value* from Fisher's exact test = 0.001), resistance to pyrazinamide (*p-value* from Fisher's exact test = 0.001) and living in urban area (crude OR=1.55, 95% CI = 1.02-2.37, *p-value* = 0.042). (Table 4.7-4.9)

Table 4.7 Comparisons of general characteristics between case and control group by univariate analysis.

Characteristics	**Case (n=189) Number (%)**	**Control (n=189) Number (%)**	**Crude OR**	**95%CI**	***p-value***
Gender					
male	143 (75.7)	139 (73.5)	1		
female	46 (24.3)	50 (26.5)	1.12	0.70-1.78	0.64
Age (year)					
< 32	47 (24.9)	46 (24.3)	1		
32-54	90 (47.6)	102 (54.0)	0.86	0.53-1.42	0.562
> 54	52 (27.5)	41 (21.7)	1.24	0.70-2.21	0.463
Education					
No formal education	158 (83.6)	175 (92.6)	1		
Educated	31 (16.4)	14 (7.4)	2.45	1.26-4.78	0.008

Table 4.7 Comparisons of general characteristics between case and control group by univariate analysis (cont.)

Characteristics	Case (n=189) Number (%)	Control (n=189) Number (%)	Crude OR	95%CI	*p-value*
Occupation					
Official/housewife	13 (6.9)	15 (7.9)	1		
Unemployed	56 (29.6)	26 (13.8)	2.49	1.04-5.97	0.042
Agriculture	41 (21.7)	59 (31.2)	0.8	0.35-1.86	0.608
Employee	68 (36.0)	75 (39.7)	1.05	0.46-2.36	0.913
Vendor	11 (5.8)	14 (7.4)	0.91	0.31-2.68	0.859
Income(Baths/month)					
> 8,000	25 (13.2)	42 (22.2)	1		
< 5,000	39 (20.6)	37 (19.6)	1.77	0.91-3.46	0.094
5,000-8,000	61 (32.3)	83 (43.9)	1.24	0.68-2.24	0.488
Missing 91 cases	64 (33.9)	27 (14.3)		Not available	
Marital status					
Married	129 (68.3)	142 (75.1)	1		
Single	49 (25.9)	41 (21.7)	1.32	0.82-2.12	0.26
Divorce and separated	11 (5.8)	6 (3.2)	2.02	0.73-5.61	0.18
Smoking during treatment					
No	140 (74.1)	156 (82.5)	1		
Yes	49 (25.9)	33 (17.5)	1.66	1.01-2.72	0.047
Smoking habit *					
Occasionally	31 (63.3)	19 (57.6)	1		
Every day	18 (36.7)	14 (42.4)	0.79	0.32- 1.94	0.605
Drinking alcohol during treatment					
No	154 (81.5)	146 (77.2)	1		
Yes	35 (18.5)	43 (22.8)	0.77	0.47-1.27	0.31
Beer					
No	165 (87.3)	161 (85.2)	1		
Yes	24 (12.7)	28 (14.8)	0.84	0.47-1.50	0.55
Wine					
No	187 (98.9)	188 (99.5)	1		
Yes	2 (1.1)	1 (0.5)	2.01	0.18-22.36	0.57

Table 4.7 Comparisons of general characteristics between case and control group by univariate analysis (cont.)

Characteristics	Case (n=189) Number (%)	Control (n=189) Number (%)	Crude OR	95%CI	*p-value*
Whisky					
No	187 (98.9)	186 (98.4)	1		
Yes	2 (1.1)	3 (1.6)	0.66	0.11- 4.01	0.66
Rice whisky					
No	174 (92.1)	176 (93.1)	1		
Yes	15 (7.9)	13 (6.9)	1.17	0.54-2.53	0.7
Local brewed whisky					
No	186 (98.4)	187 (98.9)	1		
Yes	3 (1.6)	2 (1.1)	1.51	0.25-9.13	0.66
Frequency of drinking alcohol*					
Infrequent	22 (62.9)	33 (76.7)	1		
Frequent	13 (37.1)	10 (23.3)	1.95	0.73-5.22	0.184
Drinking amount /time					
< 150-300 cc	6 (17.2)	7 (16.3)	1		
150-300 cc	18 (51.4)	16 (37.2)	1.31	0.36-4.72	0.678
> 150-300 cc	11 (31.4)	20 (46.5)	0.64	0.17-2.39	0.501

Table 4.8 Comparisons of clinical characteristics between case and control group by univariate analysis

Characteristics	Case (n=189) Number (%)	Control (n=189) Number (%)	Crude OR	95%CI	*p-value*
Concomitant disease					
No	112 (59.3)	131 (69.3)	1		
Yes	63 (33.3)	47 (24.9)	1.57	0.99-2.47	0.052
Unknown/no exam	14 (7.4)	11 (5.8)	1.49	0.65-3.41	0.347
Hypertension					
No	150 (79.4)	151 (79.9)	1		
Yes	8 (4.2)	15 (7.9)	0.54	0.22-1.23	0.169
Unknown/no exam	31 (16.4)	23 (12.2)	1.36	0.76-2.44	0.306
DM					
No	136 (72.0)	139 (73.5)	1		
Yes	22 (11.6)	19 (10.1)	1.18	0.61-2.28	0.616
Unknown/no exam	31 (16.4)	31 (16.4)	1.02	0.59-1.77	0.938
AIDS					
No	137 (72.5)	151 (79.9)	1		
Yes	30 (15.9)	22 (11.6)	1.5	0.83-2.73	0.181
Unknown/no exam	22 (11.6)	16 (8.5)	1.16	0.77-3.00	0.234
Heart disease					
No	133 (70.4)	135 (71.4)	1		
Yes	4 (2.1)	3 (1.6)	1.35	0.30-6.16	0.696
Unknown/no exam	52 (27.5)	51 (27.0)	1.04	0.66-1.63	0.882
Liver disease					
No	140 (74.1)	134 (70.9)	1		
Yes	2 (1.1)	2 (1.1)	0.96	0.19-6.89	0.965
Unknown/no exam	47 (24.9)	53 (28.0)	0.85	0.54-1.34	0.484
Kidney disease					
No	133 (70.4)	129 (68.3)	1		
Yes	2 (1.1)	1 (0.5)	1.94	0.17-21.66	0.59
Unknown/no exam	54 (28.6)	59 (31.2)	0.89	0.57-1.38	0.597
Herpes zoster					
No	64 (33.9)	54 (28.6)	1		
Yes	8 (4.2)	3 (1.6)	2.25	0.57-8.90	0.248
Unknown/no exam	117 (61.9)	132 (69.8)	0.75	0.48-1.16	0.195
Exercise during treatment					
Yes	27 (14.3)	43 (22.8)	1		
No	162 (85.7)	146 (77.2)	1.77	1.04-3.00	0.04

Table 4.8 Comparisons of clinical characteristics between case and control group by univariate analysis (cont.)

Characteristics	Case (n=189) Number (%)	Control (n=189) Number (%)	Crude OR	95%CI	*p-value*
Cavity lung lesion					
No	49 (25.9)	71 (37.6)	1		
Yes	140 (74.1)	118 (62.4)	1.72	1.11-2.67	0.016
Sputum smear status before treatment					
Positive 1+	70 (37.0)	82 (43.4)	1		
Positive 2+	41 (21.7)	47 (24.9)	1.02	0.60-1.73	0.936
Positive 3+	78 (41.3)	60 (31.7)	1.52	0.96-2.42	0.075
Sputum smear result after 2-3 months of treatment					
Negative	99 (54.4)	180 (95.2)	1		
Positive 1+	62 (32.8)	7 (3.7)	16.1	7.10-36.53	0.001
Positive 2+ and /3+	21 (11.1)	2 (1.1)	19.09	4.38-83.11	0.001
No test available	7 (3.7)	0 (0.0)		Non calculated	
Drug susceptibility testing					
No	89 (47.1)	160 (84.7)	1		
Yes	100 (52.9)	29 (15.3)	6.2	3.81-10.10	0.001
Isoniazid test					
Susceptible	59 (59.0)	26 (89.7)	1		
Resistant	22 (22.0)	1 (3.4)	9.7	1.24-75.80	0.030
Unknown	19 (19.0)	2 (6.9)	4.19	0.91-19.30	0.066
Rifampicin test **					
Susceptible	54 (54.0)	27 (93.1)		0.001	
Resistant	26 (26.0)	0 (0.0)			
Unknown	20 (20.0)	2 (6.9)			
Pyrazinamide test**					
Susceptible	62 (62.0)	20 (69.0)		0.001	
Resistant	7 (7.0)	0 (0.0)			
Unknown	31 (31.0)	9 (31.0)			
Ethambutol test					
Susceptible	60 (60.0)	21 (72.4)	1		
Resistant	13 (13.0)	1 (3.4)	4.55	0.56-36.93	0.156
Unknown	27 (27.0)	7 (24.1)	1.35	0.52-3.56	0.544
Streptomycin test					
Susceptible	39 (39.0)	11 (37.9)	1		
Resistant	6 (6.0)	1 (3.4)	1.69	0.18-15.59	0.642
Unknown	55 (55.0)	17 (58.6)	0.91	0.39-2.16	0.835

*** There was a zero cell , the Fisher exact test to calculate the association*

Table 4.9 Comparisons of environmental characteristics between case and control group by univariate analysis

Characteristics	Case (n=189) Number (%)	Control (n=189) Number (%)	Crude OR	95%CI	*p-value*
Treatment delay(days)					
< 16	44 (23.3)	42 (22.2)	1		
16-50	100 (52.9)	101 (53.4)	0.945	0.57-1.57	0.827
> 50	45 (23.8)	46 (24.3)	0.934	0.52-1.68	0.820
Residence					
Rural	112 (59.3)	131 (69.3)	1		
Urban	77 (40.7)	58 (30.7)	1.55	1.02-2.37	0.042
Living environment relative to the sea coast *					
Mainland	150 (79.4)	147 (77.8)	1		
Near Andaman sea	7 (3.7)	6 (3.2)	1.14	0.37-3.48	0.814
Near Gulf of Thailand	32 (16.9)	36 (19.0)	0.87	0.51-1.48	0.608
Distance from home to clinic					
< 4 kms	34 (18.0)	37 (19.6)	1		
4-14 kms	106 (56.1)	108 (57.1)	1.07	0.60-1.83	0.810
> 14 kms	49 (25.9)	44 (23.3)	1.21	0.65-2.25	0.542
Type of traveling to TB clinic					
Hired motorcycle					
No	161 (85.2)	173 (91.5)	1		
Yes	28 (14.8)	16 (8.5)	1.88	0.98-3.60	0.057
Taxi					
No	163 (86.2)	166 (87.8)	1		
Yes	26 (13.8)	23 (12.2)	1.15	0.63-2.10	0.646
Private vehicle					
No	148 (78.3)	157 (83.1)	1		
Yes	41 (21.7)	32 (16.9)	0.74	0.44-1.23	0.242
Walk/bicycle					
No	188 (99.5)	186 (98.4)	1		
Yes	1 (0.5)	3 (1.6)	0.33	0.03-3.20	0.339
Travel convenience					
very convenient	176 (93.6)	180 (95.7)	1		
inconvenient	12 (6.4)	8 (4.3)	1.53	0.61-3.84	0.361
DOT observer					
Public health officer	108 (57.1)	121 (64.0)	1		
Relative	61 (32.3)	51 (27.0)	1.34	0.85-2.11	0.206
Health volunteer	20 (10.6)	17 (9.0)	1.32	0.66-2.65	0.437

*Crude OR = crude odds ratio, 95%CI = 95% confidence interval, p-value of Wald statistics significant ≤ 0.05 *Yala province does not have the seacoast*

4.3 Multivariate analysis

During the multiple logistic regression analysis to determine independent factors that could predict treatment failure among new positive sputum smear TB cases, the following variables were used to enter the model (using enter method), namely, gender, age group, religion, formal education in school, occupation, income, marital status, alcohol drinking, whisky, rice whisky, local brewed whisky, smoking during treatment, exercise, concomitant disease, hypertension, heart disease, liver disease, cavity lung lesion, sputum smear results before treatment, Sputum smear result after 2-3 months of treatment, drug susceptibility testing, residence, living environment relative to the sea coast, distance from home to clinic, type of traveling, travel convenience, duration of treatment delay and DOT observer.

After the final step of multiple logistic regression analysis, four independent factors that significantly associated with treatment failure were : 1) positive sputum smear after 2-3 months of treatment (positive 1^+; adjusted OR = 15.08, 95% CI = 4.84 - 46.99) and (positive 2^+ - 3^+; adjusted OR=11.76, 95% CI =2.01-68.78), 2) having drug susceptibility testing done (adjusted OR=9.45; 95% CI =4.03-22.1), 3) living in urban area (adjusted OR = 2.44; 95% CI=1.05-5.67), and 4) having a family member as DOT observer (adjusted OR= 3.25; 95% CI = 1.33-7.93). (Table 4.10)

Table 4.10 Independent factors associated with treatment failure determined by multivariate logistic regression analysis

Factors	Univariate analysis		Multivariate analysis*		
	Crude OR	**95%CI**	**Adjusted OR**	**95%CI**	***p-value***
Sputum smear result after 2-3 months of treatment					
Negative	1.00		1.00		
Positive1^{+}	16.10	7.10-36.53	15.08	4.84-46.99	0.001
Positive 2^{+}and 3^{+}	19.09	4.39-83.11	11.76	2.01-68.78	0.006
Drug susceptibility testing					
No	1.00		1.00		
Yes	6.20	3.81-10.10	9.45	4.03-22.14	0.001
Residence					
Rural	1.00		1.00		
Urban	1.55	1.02-2.37	2.44	1.05-5.67	0.037
DOT observer					
Public health officer	1.00		1.00		
Relative	1.34	0.85-2.11	3.25	1.33-7.93	0.010

*Crude OR = crude odds ratio, 95%CI = 95% confidence interval, p-value of Wald statistics significant ≤ 0.05, Adjusted OR = adjusted odds ratio, *In the multivariate analysis, all variables in the univariate analysis did not have multicollinearity were considered*

CHAPTER V
DISCUSSION

5.1 Research methodology

The hospital-based case-control study was designed to determine the factors associated with treatment failure. Since the annual incidence of treatment failure among the patients who had DOT regimen was quite rare (only 2%). In addition, this is the research exercise for master degree thesis which should be finished within 1 year. Only retrospective study involving the patients who already registered at the TB clinic of public hospitals could be done to achieve both objectives of the study. However, various kinds of bias could occur as follows;

1. Selection bias

Since the subjects were recruited starting from the past 6 years, the subjects selected might not be perfect to deliver all the complete data required. Some problems encountered were the loss of TB registry or medical records, inability to seek the subjects due to death or loss from follow-up. Their relatives might deliver incorrect data of the subjects. Furthermore, the national TB control guideline had been changed from time to time over the past 6 years such as the recommendation to do culture and drug-susceptibility test for each new TB case in order to screen for drug resistance. Since all these two tests were recommended in the year 2005 (58), very little number of patients who had these two tests in the year before 2005 was obvious.

2. Recall bias

Since the data required related to what happened 6 years before, the informant might have difficulty trying to recall some details of their illness, for example, details about exercise frequency or amount of alcohol they drank.

5.2 Research finding

Positive sputum smear result after 2-3 months of treatment

The persistence of AFB in the sputum after the first few months of DOT treatment, either 1+ or ≥ 2+ positive, was significantly higher in the case group compared to the control group during univariate analysis with the crude OR of 16.1 (95% CI = 7.10-36.53; *p-value* = 0.001) and 19.09 (95% CI = 4.38-83.11; *p-value* = 0.001), respectively. Again, the persistence of AFB, either 1+ or 2 – 3 +, still predicted treatment failure revealed by multiple logistic regression analysis with the adjusted OR of 15.08 (95% CI = 4.84 - 46.99) and 11.76 (95% CI =2.01-68.78), respectively.

The possible explanation for these findings would be the rapid eradication of AFB organism in lung tissue within the first few months of treatment only if the effective antiTB drugs were persistently used in adequate amount (32, 33). Therefore, the causes of treatment failure might be drug resistance of the AFB organism, poor drug compliance and inability to follow the DOT guideline recommended by the health personnel. This reflected the malpractice or defect of DOT practice in the rural area.

The result of this study also agreed with what Hua Jianzhao et al. (11) reported that the persistence of AFB organism after the first few months of treatment associated with unsuccessful treatment outcomes (treatment failure, default and death) with the adjusted OR of 6.0 (95% CI = 2.3-15.9, *p-value* < 0.001).

Having drug susceptibility test (DST) done

The patients in the case group were more likely to have drug susceptibility test done compared to the subjects in control group with the crude OR of 6.2 (95%CI = 3.81-10.10; *p-value* = 0.001). Having DST done also predicted treatment failure with the adjusted OR of 9.45 (95%CI = 4.03-22.14; *p-value* = 0.001). The simple explanation of this finding was the recommendation given by the national TB control guideline issued in the year 2005 (58). According to the guideline, DST was indicated in those who were new HIV-infected TB patients, those who contacted the MDR-TB cases, those whose sputum examination revealed the persistence of AFB after the first

few months of treatment and the treatment failure subjects. As such, DST was very more likely to be done in the treatment failure subjects, i.e. the case group.

Although almost 50% of the case group did not have DST done revealed by this study, it did not mean that these subjects were not cared for according to the guideline. After discussion with local health personnel, all these patients were classified as "treatment after failure" before the DST was done. This outcome category was not included in this study and reflected up to half of the treatment failure subjects in this study did not have DST done. Another reason would be the lack of DST report due to poor technique of sputum acquisition resulting in contamination. Lack of laboratory facility to do the DST in the local hospitals was also another explanation. (26).

Nonetheless, the antiTB drug resistance (isoniazid, rifampicin and pyrazinamide) of patients was found more frequent among those who were in the case group revealed by univariate analyses. The multiple logistic regression analysis could not be used to determine these associations as one or more of the four expected cell frequencies in 2 X 2 table was less than 5 (55, 56). Very few subjects in the control group had DST done due to no indication recommended by the national guideline issued in the year 2005 (58).

The association of antiTB drug resistance and treatment failure was also reported by the study of Marcos A. et al.(9) who suggested that the DOT regimen must be used only under strict supervision and should be adapted suitably to individual patient. The major risk factors for non-cure among new TB cases were lack of DST and the occurrence of MDR-TB (11).

Higher risk of treatment failure among urban population

In this study, 40.7% and 30.7% of the case and control group lived in urban area. After univariate analysis, living in urban area associated with treatment failure (crude OR = 1.55; 95% CI = 1.02-2.37; *p-value* = 0.042), compared to living in rural area. The multivariate analysis also showed the significant increased risk of this exposure (adjusted OR = 2.44; 95% CI = 1.05-5.67; p-value = 0.037). There were many reasons behind this finding. Firstly, the patients who lived in the urban area had to go outside to work and earned their living. It was impossible for them to practice

DOT regimen by visiting the local health personnel nearly everyday. Secondly, the urban hospitals were more likely to be crowded compared to the rural hospitals. This perceived barrier certainly affected their regular visits to the urban hospitals. Thirdly, the urban environment would be adversely affected by pollution, poor ventilation, immigration and lack of accommodation. This finding was also found by the study of Abubakar I, et al. (59) who explained that the complexity of urban society, lack of accommodation and drug addiction might be the underlying cause of incomplete DOT regimen (loss follow-up, transfer out, poor drug compliance and death).

However, this finding did not agree with the study in West Bengal, India (39) which found that living in urban area did not associate with treatment failure. This might be the difference of health infrastructure between India and Thailand.

Having relatives as DOT observer

In this study, 32.3% and 27.0% of the case and control group had their relatives as DOT observer. After univariate analysis, having relatives as DOT observer did not significantly associate with treatment failure (crude OR = 1.34; 95% CI = 0.85-2.11; *p-value* = 0.206). On the other hand, multivariate analysis showed statistically significant association of this factor with treatment failure (adjusted OR = 3.25; 95% CI = 1.33-7.92; *p-value* = 0.01). The possible explanation would be those who tended not to comply with taking antiTB drugs under closed supervision of local health personnel would choose to be supervised by their own relatives. Their perceived barriers might be lack of time to see local health personnel everyday, inconvenient travel and the long distance between home and the TB clinic. The patients were much familiar with their own relatives and certainly the power of direct authorization between the patients and their relatives would be weak.

Nonetheless, the finding of this study was consistent with those reported by Pima W. (51) who found that relapsing cases and having relatives as DOT observer associated with treatment failure but without statistical significance (crude OR = 3.1; 95%CI = 0.70-14.3). However, the relatives could be efficient DOT observes only if they were properly trained and adequate social support was also provided (60). The study by Siripanichgon K. et al (50) also emphasized the critical importance of taking antiTB drugs by the patients under direct supervision of health personnel or trained

health volunteer in DOT regimen. Using the patients' relatives as DOT observer was unacceptable as they might not do their jobs efficiently enough.

5.3 Limitation of the study

1. Since interview using the structured questionnaire was also a part of data collection, some subjects were not available due to the retrospective study design. Therefore, incorrect answers might be given by the informants resulting in incorrect interpretation and, finally, the results of the study.

2. The relationship between the resistance of TB organisms to antiTB drugs and treatment failure could not be analyzed by multiple logistic regression analysis due to too small sample size in the control group.

3. Since the subjects were recruited over the past 6 years, missing data or incomplete record was, therefore, unavoidable.

CHAPTER VI
CONCLUSION AND RECOMMENDATION

This 6-year retrospective research recruited the new smear-positive pulmonary TB patients registered between October 2004 – September 2010 who lived in seven provinces (Songkhla, Yala, Pattani, Narathiwat, Trang, Phatthalung and Satun) of the lower southern part of Thailand. The objective was to determine factors associated with treatment failure among these patients who received DOT regimen. The 12th TB center Yala and 45 government hospitals participated the study. Data was collected during May 2012 - August 2012. Three hundred and seventy eight subjects were finally recruited with the ratio of case to control of 1:1. One hundred and eighty nine cases were allocated in the case (treatment failure) group and similarly in the control (cure) group. The distribution of subjects in the province of Songkhla, Yala, Pattani, Narathiwat, Trang, Phatthalung and Satun were 43.90%, 14.8%, 13.8%, 9.5%, 7.4%, 6.3% and 4.2% respectively.

6.1 Conclusions

Regarding the general characteristics of the case group, more than half of the subjects were male (75.7%). The number of subjects in the age group of 32-54 years old, more than 54 years old and less than 32 years old were 47.6 %, 27.5% and 24.9%, respectively. (median = 45 years; IQR = 11 years). The majority of subjects were educated in formal school and married. The number of subjects classified by type of occupation were employee (36%), unemployed (29.6%) and agriculture (21.7%). The majority of the subjects had income per month as 5,000-8,000 THB 32.3%, less than 5,000 THB 20.6% and more than 8,000 THB 13.2%. (median = 7,000 THB; IQR = 3,000 THB).

Regarding the general characteristics of the control group, More than half of the subjects were male (73.5%). The number of subjects in the age group of 32-54 years old, more than 54 years old and less than 32 years old were 54.0 %, 24.3% and 21.7%, respectively (median = 42 years; IQR = 22 years). The majority of subjects were educated in formal school and married. The number of subjects classified by type of occupation were employee (39%), agriculture (31.2%) and unemployed (13.8%). The majority of the subjects had income per month as 5,000-8,000 THB 43.9%, more than 8,000 THB 22.2% and less than 5,000 THB 19.6% (median = 7,000 THB; IQR = 3,250 THB).

Following the univariate analysis, the significant factors associated with treatment failure were as follows:

1. No formal education (crude OR = 2.45, 95% CI = 1.26-4.78)
2. Unemployed (crude OR = 2.49, 95% CI = 1.04-5.97)
3. Smoking during treatment (crude OR = 1.66, 95% CI = 1.01-2.72)
4. No exercise during treatment (crude OR=1.77, 95% CI = 1.04-3.00)
5. Having cavity lung lesion (crude OR = 1.72, 95% CI = 1.11-2.67)
6. Positive sputum smear after 2-3 months of treatment
   - positive 1^+ (crude OR = 16.1, 95% CI = 7.10-36.53)
   - positive 2^+/ 3^+(crude OR = 19.09, 95% CI = 4.38-83.11)
7. Having drug susceptibility test done
   (crude OR = 6.2; 95% CI = 3.81-10.10)
8. Resistance to isoniazid (crude OR = 9.70, 95% CI = 3.81-10.10)
9. Resistance to rifampicin (*p-value* from Fisher's exact test = 0.001)
10. Resistance to pyrazinamide (*p-value* from Fisher's exact test = 0.001)
11. Living in urban area (crude OR = 1.55, 95% CI = 1.02-2.37)

Following the multivariate analysis, four factors significantly associated with treatment failure as shown :

1. Positive sputum smear after 2-3 months of treatment
   - positive 1^+; adjusted OR = 15.08, 95% CI = 4.84 - 46.99
   - positive 2^+- 3^+; adjusted OR=11.76, 95% CI =2.01-68.78

2. Having drug susceptibility test done
   (adjusted OR=9.45; 95% CI = 4.03 - 22.1)
3. Living in urban area (adjusted OR = 2.44; 95% CI=1.05-5.67)
4. Having a family member as DOT observer
   (adjusted OR= 3.25; 95% CI=1.33-7.93).

6.2 Recommendation

6.2.1 Recommendation from the study results

1) Since TB control in the urban area was more difficult than in the rural area. For those whose sputum examination still showed the persistence of AFB at the end of the second to the third month of DOT regimen, intensive measures must be implemented in this most vulnerable group. They are very likely to end up with treatment failure. The local health personnel in charge is directly responsible for the efficient control of TB epidemics. Moreover, patient referral system, the co-ordination between various organizations and the community network must be strengthened. Intensive and active activities initiated by the public health sector must also be implemented.

2) Drug sensitivity test must be done in all patients indicated in the national guideline issued in the year 2005. As a result, drug resistance and treatment failure are likely to be decreased.

3) All kinds of DOT observer, namely, local health personnel, health volunteer or the patients' relatives must be trained to strictly follow the requirement of DOT regimen.

6.2.2 Recommendation for future study

1) This kind of research should be repeated in the national level to recruit more subjects. Cohort study design would be the best methodology to collect all the necessary data without any missing value.

2) The evaluation of knowledge and attitude toward DOT treatment of various kinds of DOT observers should also be done in order to find the specific defects within each kind of DOT observes.

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APPENDIX

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Certificate of Approval

COA no. Si 171/2012

Protocol Title : Selected risk factors associated with treatment failure among new smear-positive pulmonary tuberculosis patients from seven provinces in the lower southern part of Thailand.

Protocol number : 094/2555(EC1)

Principal Investigator/Affiliation : Mr.Thawatchai Luankaew / Department of Preventive and Social Medicine Faculty of Medicine Siriraj Hospital, Mahidol University

Research site : Faculty of Medicine Siriraj Hospital

Approval includes :

1. SIRB Submission Form
2. Proposal
3. Telephone Script and Verbal Informed Consent
4. Case Record Form
5. Principle Investigator's curriculum vitae

Approval date : March 21, 2012

Expired date : March 20, 2013

This is to certify that Siriraj Institutional Review Board is in full Compliance with international guidelines for human research protection such as the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

(Prof. Jarupim Soongswang, M.D.)
Chairperson

March 21, 2012
date

(Clin. Prof. Udom Kachintorn, M.D.)
Dean of Faculty of Medicine Siriraj Hospital

27 MAR 2012
date

หน่วยพิมพ์โรงพยาบาลศิริราช 2341 / 3,000 แผ่น / ก.ย 51 / Mat. 10023252

บันทึกข้อความ

ส่วนราชการ โรงพยาบาลหาดใหญ่ กลุ่มการพยาบาล งานห้องผ่าตัด โทร ๑๗๗๒

ที่ สข ๐๐๒๗.๑๐๗/พิเศษ **วันที่** 21 **เดือน** มิ.ย. **พ.ศ.** 55

เรื่อง รายงานผลการพิจารณางานวิจัยด้านจริยธรรม ครั้งที่........./๒๕๕๔

เรียน หัวหน้าพยาบาลโรงพยาบาลหาดใหญ่

ตามที่ คณะกรรมการประเมินงานวิจัยด้านจริยธรรมกลุ่มการพยาบาล โรงพยาบาลหาดใหญ่ ได้รับมอบหมายให้ดำเนินการประเมินงานวิจัยด้านจริยธรรม เพื่อประกอบการพิจารณาอนุญาตให้ผู้วิจัยเก็บข้อมูล จากผู้ป่วยหรือบุคลากรของโรงพยาบาลหาดใหญ่นั้น ในการนี้ขอรายงานผลการพิจารณาโครงร่างวิจัยของ

คุณ ทวัชชัย ล้วนแก้ว จาก มหาวิทยาลัยมหิดล สาขาวิชาระบาดวิทยา คณะแพทยศาสตร์ ศิริราช

เรื่อง ปัจจัยที่ทำให้ผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อ ที่ผลการรักษาล้มเหลว ในจ.ว. ภาคใต้ตอนล่างของประเทศไทย

มีดังต่อไปนี้...

.... ได้ขอความแนะนำแล้ว

สรุปแล้ว ☑ อนุญาตให้เก็บข้อมูลเพื่อการวิจัยได้ 6 ก.ค. 55 เนื่องจากได้แก้ไขวิธีการเก็บรวบรวมข้อมูล ด้านพิทักษ์สิทธิ์

☑ ไม่อนุญาตให้เก็บข้อมูลเพื่อการวิจัย เนื่องจาก การเข้าถึงกลุ่มเป้าหมายไม่ถูกต้องตามหลักการพิทักษ์สิทธิ์กลุ่มเป้าหมาย - ไม่มีใบแสดงความยินยอมเข้าร่วมการวิจัยของกลุ่มเป้าหมาย ฯลฯ

จึงเรียนมาเพื่อโปรดพิจารณา เห็นควรอนุญาต

(ลงชื่อ) ....
(น.ส.ธรทิพย์ ...)
กรรมการประเมินงานวิจัยด้านจริยธรรมฯ

(ลงชื่อ) ....
(นางคิดชนก อนุชาญ)
ประธานกรรมการประเมินงานวิจัยด้านจริยธรรมฯ

ขอให้ผู้วิจัยทำข้อตกลงกับกลุ่มการพยาบาลโรงพยาบาลหาดใหญ่ ดังนี้

๑. ผู้วิจัยจะมอบรายงานวิจัยฉบับสมบูรณ์เรื่องนี้แก่กลุ่มการพยาบาลฯ ☑ ยินดี ☐ ไม่ให้สัญญา

๒. ผู้วิจัยจะยินดีเป็นที่ปรึกษาให้คำแนะนำเรื่องนี้แก่บุคลากรกลุ่มการพยาบาล ☑ ยินดี ☐ ไม่ให้สัญญา

๓. ผู้วิจัยจะปฏิบัติตามขั้นตอนการขออนุญาต การชี้แจง การพิทักษ์สิทธิ์อย่างเคร่งครัด ☑ ยินดี ☐ ไม่ให้สัญญา

☑ ยินดีทำตามข้อตกลง ☐ ไม่ให้สัญญา

(ลงชื่อ) ....
(นายทวัชชัย ล้วนแก้ว)
ผู้วิจัย

☑ อนุมัติ ☐ ไม่อนุมัติ

(ลงชื่อ) ....
(นางปริศนา ...)
หัวหน้าพยาบาลโรงพยาบาลหาดใหญ่

โรงพยาบาลตรัง
๖๙ ถ.โคกขัน ต.ทับเที่ยง อ.เมือง จ.ตรัง ๙๒๐๐๐
โทร ๐๗๕ - ๒๑๘๐๑๘ โทรสาร ๐๗๕ – ๒๑๗๑๗๙

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เอกสารรับรองโดยคณะกรรมการจริยธรรมการวิจัยในคน โรงพยาบาลตรัง

เลขที่ .....๐๕๒/๒๕๕๕.....

ชื่อโครงการ	ปัจจัยคัดสรรที่ทำให้ผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อ ที่ผลการรักษาล้มเหลว ใน ๗ จังหวัดภาคใต้ตอนล่างของประเทศไทย
เลขที่โครงการ/รหัส	ID ๐๕๒/๐๖-๒๕๕๕
ชื่อหัวหน้าโครงการ	นายธวัชชัย ล้วนแก้ว
ที่ทำงาน	คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

ขอรับรองว่าโครงการดังกล่าวข้างต้น ได้ผ่านการพิจารณาเห็นชอบโดยสอดคล้องกับแนวปฏิญญาเฮลซิงกิ จากคณะกรรมการจริยธรรมการวิจัยในคน โรงพยาบาลตรัง

ลงนาม .....
(นายอุกฤษฎ์ คุณาธรรม)
ประธานคณะกรรมการจริยธรรมการวิจัยในคน

ลงนาม .....
(นายชัยยุทธ ศักดิ์ศรชัย)
ผู้อำนวยการโรงพยาบาลตรัง

วันที่รับรอง..... 4 ก.ค. 2555

ID □□□

บทสมภาษณ์ทางโทรศัพท์ และการได้รับความยินยอมด้วยวาจา

(telephone script and verbal informed consent)

ชื่อโครงการวิจัย (ภาษาไทย) "ปัจจัยคัดสรรที่ทำให้ผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อมีผลการรักษาล้มเหลว ใน 7 จังหวัดภาคใต้ตอนล่างของประเทศไทย"

Title of protocol (English) "Selected risk factors associated with treatment failure among new smear-positive pulmonary tuberculosis patients from seven provinces in the lower southern part of Thailand."

ชื่อหัวหน้าโครงการวิจัย นายธวัชชัย ล้วนแก้ว(Mr.Thawatchai Luankaew)
นักศึกษาปริญญาโท สาขาวิทยาการระบาด สังกัดภาควิชาเวชศาสตร์ป้องกันและสังคม
คณะแพทยศาสตร์ศิริราชพยาบาล หมายเลขโทรศัพท์ที่ติดต่อได้ทั้งในและนอกเวลาราชการ 083-5238668

. . . . . .

Telephone script

" สวัสดีครับ ผมชื่อธวัชชัย ล้วนแก้ว เป็นนักศึกษานักศึกษาปริญญาโท สาขาวิทยาการระบาด คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล ผมอยากจะขอเวลาท่านสัก 10 นาที เพื่อถามคำถามเกี่ยวกับการรักษาวัณโรคของท่านที่ผ่านมาครับ ข้อมูลส่วนหนึ่งเราได้รับอนุญาตจากผู้อำนวยการโรงพยาบาลที่ท่านเคยเข้ารับการรักษาวัณโรค ในระหว่างการสัมภาษณ์ หากท่านต้องการหยุดการสัมภาษณ์เมื่อใดก็ตาม โปรดแจ้งให้เราทราบและทางผู้สัมภาษณ์จะหยุดการสัมภาษณ์ตามที่ท่านต้องการนะครับ"

" ผมทำการสัมภาษณ์ในครั้งนี้ มีวัตถุประสงค์เพื่อทำวิจัยเรื่องปัจจัยที่ทำให้ผู้ป่วยวัณโรคมีผลการรักษาล้มเหลว ในพื้นที่ 7 จังหวัดภาคใต้ตอนล่าง ประกอบด้วย ตรัง พัทลุง สตูล สงขลา ปัตตานี ยะลา และ นราธิวาส เพื่อให้ผู้ที่ทำงานด้านวัณโรคสามารถนำผลการศึกษาไปวางแผนการดำเนินงานเพื่อลดการแพร่กระจายของเชื้อวัณโรคในชุมชนครับ "

ID ☐☐☐

" สิ่งที่ผมอยากจะถามท่านประกอบด้วยข้อคำถามประมาณ 9 ข้อ ซึ่งเป็นข้อคำถามที่ท่านสามารถตอบได้โดยไม่ส่งผลในด้านลบต่อจิตใจอย่างรุนแรง"

"โดยข้อมูลที่ได้จากการสัมภาษณ์ในครั้งนี้จะเป็นความลับ เผยแพร่และตีพิมพ์ข้อมูลในภาพรวมโดยไม่ปรากฏชื่อของท่านนะครับ"

" ท่านยินดีที่จะให้ผมสัมภาษณ์ได้หรือไม่ครับ"

☐ **1.อาสาสมัครยินยอมให้สัมภาษณ์ด้วยวาจา (verbal consent)**

☐ **2.อาสาสมัครไม่ยินยอม**

(เมื่ออาสาสมัครยินยอม จึงดำเนินการสัมภาษณ์ บันทึกข้อมูลในแบบสัมภาษณ์จนครบทุกข้อ โดยมีพยานรับรู้)

1. " ในขณะที่ท่านป่วยด้วยวัณโรคท่านจบการศึกษาในระดับใดครับ"

.....

2. " และในตอนนั้นท่านประกอบอาชีพอะไร"

.....

3. " ท่านได้รับรายได้จากการประกอบอาชีพนั้นเดือนละเท่าไหร่ครับ"

จำนวนเงิน.....บาท

4. " ในระหว่างที่ท่านเข้ารับการรักษาวัณโรคอยู่นั้นท่านดื่มสุราหรือไม่ครับ"

.....

" ถ้าท่านดื่มสุรา ท่านดื่มนานๆครั้งเวลาเข้าสังคม หรือดื่มเป็นประจำครับ"

.....

" ท่านดื่มสุราหรือเหล้าชนิดใดบ้างครับ"

.....

ID □□□

" ปกติท่านดื่มสุราหรือเหล้าทุกวันหรือเปล่าครับ"

.....

" ในแต่ละครั้งที่ดื่ม ปริมาณมากน้อยแค่ไหนครับ"

.....

5. " ในระหว่างที่รักษาวัณโรคอยู่นั้นท่านสูบบุหรี่ด้วยหรือเปล่าครับ"

.....

" ท่านสูบบ่อยแค่ไหนครับ"

.....

" ในระหว่างที่รับการรักษาอยู่นั้น ถ้าท่านสูบบุหรี่ทุกวัน เฉลี่ยแล้ววันละกี่มวนครับ"

.....

6. " ในระหว่างการรักษาวัณโรคท่านได้ออกกำลังกายหรือไม่คับ"

.....

" ถ้าท่านได้ออกกำลังกาย ท่านออกสัปดาห์ละกี่วัน วันละกี่นาทีครับ"

.....

7. " ในบ้านของท่านมีใครป่วยเป็นวัณโรคมาก่อนหรือไม่ครับ"

.....

8. " ขณะที่ท่านรักษาวัณโรค ท่านอาศัยอยู่ในเขตเมืองหรือเขตชนบทครับ"

.....

" หมู่บ้านหรือชุมชนที่ท่านอาศัยอยู่ อยู่ติดชายทะเล หรือชายป่าหรือไม่ครับ"

.....

"บ้านของท่านที่อยู่ติดชายทะเลหรือชายป่า อยู่ทางฝั่งอันดามันหรือฝั่งอ่าวไทยครับ"

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ID □□□

9. “ จากบ้านท่านถึงโรงพยาบาลห่างกันกี่กิโลเมตรครับ”

.....

“ และท่านใช้พาหนะอะไรบ้างในการเดินทางมารับการรักษาที่โรงพยาบาล”

.....

“ ท่านคิดว่าการเดินทางสะดวกหรือไม่ที่ต้องมารับการรักษาที่โรงพยาบาลเป็นประจำ”

.....

การสัมภาษณ์ในครั้งนี้ได้รับอนุญาตจากผู้ให้สัมภาษณ์ด้วยวาจา โดยมีบุคคลต่อไปนี้เป็นพยานรับรู้

(.....) (.....)

ผู้สัมภาษณ์ พยาน

วันที่.....เดือน.....พ.ศ. 2555 วันที่.....เดือน.....พ.ศ. 2555

ID □□□

เครื่องมือที่ใช้ในการเก็บรวบรวมข้อมูล
เรื่อง ปัจจัยคัดสรรที่ทำให้ผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อ มีผลการรักษาล้มเหลว ใน 7 จังหวัดภาคใต้ตอนล่างของประเทศไทย

วัตถุประสงค์

เพื่อศึกษาปัจจัยที่ทำให้ผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อ มีผลการรักษาล้มเหลว ใน 7 จังหวัดภาคใต้ตอนล่างของประเทศไทย

คำชี้แจง

การวิจัยครั้งนี้ เป็นการศึกษาย้อนหลังเพื่อหาสาเหตุของปัญหาโดยการสัมภาษณ์ผู้ป่วยวัณโรคปอดรายใหม่เสมหะพบเชื้อที่มีผลการรักษา(treatment outcome) ล้มเหลว และ รักษาหาย ด้วยระบบยาระยะสั้นแบบสังเกตโดยตรง (DOTS) ตั้งแต่วันที่ 1 ตุลาคม 2547 – 30 กันยายน 2553 ใน 7 จังหวัด ทางภาคใต้ตอนล่างของประเทศไทย ประกอบด้วย ตรัง พัทลุง สตูล สงขลา ปัตตานี ยะลา และ นราธิวาส รวม 384 ราย ข้อมูลที่ได้จะเป็นความลับ วิเคราะห์และนำเสนอในภาพรวม เพื่อใช้ในการพัฒนางานควบคุมวัณโรค จึงขอความร่วมมือจากท่านโปรดให้คำตอบตามความเป็นจริง และขอขอบคุณผู้ที่มีส่วนเกี่ยวข้องทุกๆท่าน

เครื่องมือที่ใช้ในการเก็บรวบรวมข้อมูล แบ่งออกเป็น 2 ส่วน ประกอบด้วย

ส่วนที่ 1 แบบบันทึกข้อมูล
ส่วนที่ 2 แบบสัมภาษณ์

ID □□□

ส่วนที่ 1 แบบบันทึกข้อมูล

<u>คำชี้แจง</u> โปรดทำเครื่องหมาย √ ลงใน □ และ/ หรือ เติมข้อความลงในช่องว่างตามความเป็นจริง

ผลการรักษาวัณโรคครั้งแรก □1.ล้มเหลว(Failure) □2.หาย(Cure) รับการรักษาที่โรงพยาบาล.....อำเภอ.....จังหวัด..... โทร..... ชื่อผู้บันทึกข้อมูล.....วันที่..... โทร.....		
ประวัติการรักษาวัณโรค		
1	เพศ □ 1.ชาย □ 2.หญิง	
2	อายุ.....ปี (จำนวนปีเต็มขณะเข้ารับการรักษาวัณโรค)	
3	การนับถือศาสนา □ 1.พุทธ □ 2.อิสลาม □ 3.อื่นๆ ระบุ.....	
4	สถานภาพสมรส □ 1.โสด □ 2.สมรส □ 3.หม้าย/หย่า/แยก	
5	วัน เดือน ปี ที่เริ่มรักษา...../...../.....	
6	วัน เดือน ปี ที่เริ่มป่วย ก่อนได้รับการรักษาวัณโรค...../...../.....	
7	ประวัติการเจ็บป่วยด้วยโรคเรื้อรัง(ตอบได้มากกว่า 1 ข้อ) □ 1.มี □ 2.ไม่มี □ 3.ไม่ได้ตรวจ โรคความดันโลหิตสูง □ 1.มี □ 2.ไม่มี □ 3.ไม่ได้ตรวจ โรคเบาหวาน □ 1.มี □ 2.ไม่มี □ 3.ไม่ได้ตรวจ โรคเอดส์ □ 1.มี □ 2.ไม่มี □ 3.ไม่ได้ตรวจ หัวใจและหลอดเลือด	

ID □□□

7(ต่อ)	□ 1.มี □ 2.ไม่มี □ 3.ไม่ได้ตรวจ โรคตับ □ 1.มี □ 2.ไม่มี □ 3.ไม่ได้ตรวจ โรคไต □ 1.มี □ 2.ไม่มี □ 3.ไม่ได้ตรวจ อื่นๆ ระบุ).....	
8	ลักษณะแผลโพรงในปอดที่เห็นด้วยตาจากฟิล์มเอ็กซเรย์ □ 1.ปอดไม่มีแผลโพรง □ 2.ปอดมีแผลโพรง □ 3.ไม่ได้ตรวจ	
9	ปริมาณเชื้อที่พบในเสมหะก่อนการรักษา □ 1.พบเชื้อ 1+ □ 2.พบเชื้อ 2+ □ 3.พบเชื้อ 3+	
10	ผลการตรวจเสมหะเมื่อสิ้นสุดระยะเข้มข้น(เดือนที่ 2 หรือ 3) □ 1.ผลเป็นลบ □ 3.ตรวจแต่ไม่ทราบผล □ 2.ผลเป็นบวก □ 4.ไม่ได้ตรวจ	
11	ถ้าผลการตรวจเสมหะในข้อที่ 16 เป็นบวก ปริมาณเชื้อที่พบ □ 1.พบเชื้อ 1+ □ 2.พบเชื้อ 2+ □ 3.พบเชื้อ 3+	
12	ทำ DOTS โดย □ 1.เจ้าหน้าที่สาธารณสุข □ 2.อาสาสมัครสาธารณสุข □ 3.ญาติ เกี่ยวข้องเป็น..... □ 4.อื่นๆระบุ.....	

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13	การทดสอบความไวของเชื้อต่อยารักษาวัณโรค ☐ 1.ไม่ได้ทดสอบ ☐ 2.ได้ทดสอบ	
14	ผลการทดสอบคือ Isonizid ☐1. ดื้อ ☐2.ไม่ดื้อ ☐3.ไม่ทราบ ☐4.ไม่ได้ทดสอบ Rifampicin ☐1. ดื้อ ☐2.ไม่ดื้อ ☐3.ไม่ทราบ ☐4.ไม่ได้ทดสอบ Pyrazinamide ☐1. ดื้อ ☐2.ไม่ดื้อ ☐3.ไม่ทราบ ☐4.ไม่ได้ทดสอบ Ethambutal ☐1. ดื้อ ☐2.ไม่ดื้อ ☐3.ไม่ทราบ ☐4.ไม่ได้ทดสอบ Streptomycin ☐1. ดื้อ ☐2.ไม่ดื้อ ☐3.ไม่ทราบ ☐4.ไม่ได้ทดสอบ	
15	วัน เดือน ปี ที่จำหน่ายออกจากทะเบียน...../...../.....	

ID □□□

ส่วนที่ 2 แบบสัมภาษณ์

คำชี้แจง โปรดทำเครื่องหมาย √ ลงใน □ และ/ หรือ เติมข้อความลงในช่องว่างตามความเป็นจริง

1	ระดับการศึกษาของผู้ป่วย □ 1.ไม่ได้เรียนหนังสือ □ 2.ประถมศึกษา □ 3.มัธยมศึกษาต้อนต้น □ 4.มัธยมศึกษาตอนปลาย □ 5.ปวส./อนุปริญญา □ 6.ปริญญาตรี หรือสูงกว่า	
2	อาชีพของผู้ป่วย □ 1.ไม่ได้ประกอบอาชีพ □ 2.นักเรียน/นักศึกษา □ 3.เกษตรกรรม □ 4.รับจ้างรายวัน/กรรมกร □ 5.ค้าขาย □ 6.รัฐวิสาหกิจ/ข้าราชการ □ 7.ลูกจ้างประจำ/พนักงานบริษัทเอกชน □ 8.อื่นๆ ระบุ.....	
3	รายได้เฉลี่ยต่อเดือน(ระบุ).....บาท	
4	ในระหว่างรับการรักษาวัณโรคผู้ป่วยดื่มสุราหรือไม่ □ 1.ไม่ดื่ม □ 2.ดื่ม □ 1.ดื่มนานๆครั้งเวลาเข้าสังคม □ 2.ดื่มเป็นประจำ ชนิดของเครื่องดื่มแอลกอฮอล์(ตอบได้มากกว่า 1 ข้อ) □ 1.เบียร์ □ 2.ไวน์ □ 3.วิสกี้ □ 4.เหล้าขาว □ 5.อื่นๆระบุ..... ความถี่ของการดื่ม □ 1.ช่วงวันหยุดสุดสัปดาห์ □ 2.ทุก 2 – 3 วัน □ 3.ทุกวัน โปรดระบุปริมาณที่ดื่ม/ครั้ง □ 1.จำนวน.....กึ๊ง (1 แก้วเล็ก) □ 2.จำนวน.....กั๊ก (ครึ่งขวดแบน) □ 3.จำนวน.....แบน □ 4.จำนวน.....กลม/ขวด	

ID ☐☐☐

5	ในระหว่างการรักษาวัณโรคท่านสูบบุหรี่หรือไม่ ☐ 1.ไม่สูบ ☐ 2.สูบ ☐ 1.สูบเป็นบางครั้ง ☐ 2.เคยสูบแต่เลิกระหว่างการรักษา ☐ 3.สูบทุกวัน ระบุ.....มวน/วัน	
6	ในระหว่างการรักษาวัณโรคท่านออกกำลังกายหรือไม่ ☐ 1.ไม่ ☐ 2.ออกกำลังกาย สัปดาห์ละ.....วัน วันละ.....นาที	
7	ในบ้านของผู้ป่วยมีญาติเป็นวัณโรคมาก่อนหรือไม่ ☐ 1.มี ☐ 2.ไม่มี	
8	ลักษณะภูมิประเทศของผู้ป่วยเป็นอย่างไร ท่านอาศัยอยู่ในเขต ☐ 1.เมือง ☐ 2.ชนบท หมู่บ้านหรือชุมชนที่ท่านอาศัย อยู่ติดทะเล หรือชายป่า หรือไม่ ☐ 1.ไม่ ☐ 2.อยู่ติดทะเล หรือชายป่า ☐ 1.ฝั่งอันดามัน ☐ 2.ฝั่งอ่าวไทย	
9	ระยะทางในการเดินทางมารับการรักษาจากบ้านถึงโรงพยาบาล ประมาณ(ระบุ).....กิโลเมตร พาหนะที่ใช้ในการเดินทางมารับการรักษา(ตอบได้มากกว่า 1 ข้อ) ☐ 1.มอเตอร์ไซค์รับจ้าง ☐ 2.รถยนต์รับจ้าง ☐ 3.รถส่วนตัว ☐ 4.อื่นๆ ระบุ.....	

ID □□□

9(ต่อ)	ท่านคิดว่าการมาติดตามรับการรับยาที่สถานพยาบาลเป็นประจำ มีอุปสรรคในการเดินทางมากน้อยเพียงใด □ การคมนาคมสะดวกมาก □ การคมนาคมไม่ค่อยสะดวก เช่น ต้องใช้พาหนะหลายทอด การคมนาคมลำบาก	

ขอขอบคุณทุกท่านที่ให้ความร่วมมือเป็นอย่างดี

ธวัชชัย ล้วนแก้ว
นักศึกษาปริญญาโท สาขาวิทยาการระบาด
คณะแพทยศาสตร์ศิริราชพยาบาล
มหาวิทยาลัยมหิดล

หนังสือแสดงเจตนายินยอมเข้าร่วมโครงการวิจัย

(Informed Consent Form)

วันที่..... เดือน..... พ.ศ. 2555

ข้าพเจ้า..... อายุ.....ปี
อาศัยอยู่บ้านเลขที่.....ถนน.....ตำบล.....
อำเภอ.....จังหวัด.....รหัสไปรษณีย์.....
โทรศัพท์ .....ขอแสดงเจตนายินยอมเข้าร่วมโครงการวิจัยของ นายธวัชชัย ล้วนแก้ว
เรื่อง "ปัจจัยคัดสรรที่ทำให้ผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อ มีผลการรักษาล้มเหลว ใน 7 จังหวัดภาคใต้ตอนล่างของประเทศไทย" ซึ่งดำเนินการเก็บข้อมูลผู้เข้าร่วมการวิจัยที่คลินิกวัณโรค โรงพยาบาลของรัฐใน 7 จังหวัดภาคใต้ตอนล่าง ประกอบด้วยจังหวัด ตรัง พัทลุง สตูล สงขลา ยะลา ปัตตานี และนราธิวาส โดยสามารถติดต่อผู้วิจัยทั้งในและนอกเวลาราชการทางโทรศัพท์หมายเลข 083 – 5238668โครงการวิจัยนี้ทำขึ้นเพื่อวิเคราะห์ปัจจัยด้านระบาดวิทยาที่ทำให้ผู้ป่วยวัณโรคปอดรายใหม่ที่เสมหะพบเชื้อ มีผลการรักษาล้มเหลว ใน 7 จังหวัดภาคใต้ตอนล่างของประเทศไทย ใช้ระยะเวลาในการศึกษาตลอดทั้งโครงการ 1 ปี 6 เดือน โดยไม่มีทุนวิจัย ผลที่คาดว่าจะได้รับจากการวิจัยนี้ สามารถนำไปใช้วางแผนดำเนินงานควบคุมวัณโรค ป้องกันความยุ่งยากสิ้นเปลืองในการรักษาวัณโรคดื้อยาและลดการแพร่กระจายของโรคในชุมชน

ข้าพเจ้าได้รับเชิญให้เข้าร่วมการวิจัยนี้เพราะเคยเป็นผู้ป่วยวัณโรคปอดรายใหม่เสมหะพบเชื้อ ที่ขึ้นทะเบียนรักษาโดยมีพี่เลี้ยงกำกับการกินยา ณ โรงพยาบาลหาดใหญ่ อำเภอหาดใหญ่ จังหวัดสงขลา ซึ่งขณะนั้นข้าพเจ้ามีอายุมากกว่า 18 ปีบริบูรณ์ โดยมีผู้เข้าร่วมการวิจัยใน 7 จังหวัดภาคใต้ตอนล่างประมาณ 384 ราย แบ่งเป็น 2 กลุ่มในอัตราส่วน 1: 1 คือ กลุ่มผู้ป่วยวัณโรคปอดรายใหม่เสมหะพบเชื้อที่มีผลการรักษาล้มเหลว กับกลุ่มผู้ป่วยวัณโรคปอดรายใหม่เสมหะพบเชื้อที่มีผลการรักษาหาย และเป็นการศึกษาผู้ที่มีผลการรักษาย้อนหลังตั้งแต่วันที่ 1 ตุลาคม 2547 – 30 กันยายน 2553

-หากข้าพเจ้าตัดสินใจเข้าร่วมการวิจัยแล้ว ข้าพเจ้ายินยอมให้ผู้วิจัยดำเนินการคัดลอกข้อมูลที่เป็นประวัติการรักษา รวมทั้งบันทึกทางการแพทย์ที่เกี่ยวข้อง และยินยอมตอบคำถามจากการสัมภาษณ์จำนวน 1 ครั้ง ตามความเป็นจริงทุกประการ โดยอาจจะมีความเสี่ยงเกิดขึ้นจากการสัมภาษณ์ผู้เข้าร่วมการวิจัย เช่น อาจรู้สึกหงุดหงิดรำคาญ ไม่พึงพอใจ ถ้าต้องตอบคำถามเป็นเวลานาน ดังนั้นเวลาในการสัมภาษณ์คาดว่าจะใช้เวลาไม่เกิน 10 นาที

-หากข้าพเจ้าไม่เข้าร่วมในโครงการวิจัยนี้ ข้าพเจ้าก็จะได้รับการตรวจเพื่อการวินิจฉัยและรักษาโรคของข้าพเจ้าในครั้งต่อไปตามวิธีการที่เป็นมาตรฐานสากล

หากมีข้อข้องใจที่จะสอบถามเกี่ยวข้องกับการวิจัย หรือหากเกิดผลข้างเคียงที่ไม่พึงประสงค์จากการวิจัย ข้าพเจ้าสามารถติดต่อ นายธวัชชัย ล้วนแก้ว หมายเลขโทรศัพท์ 083-5238668
ในการเข้าร่วมการวิจัยครั้งนี้ข้าพเจ้าจะไม่ได้รับค่าตอบแทน และไม่มีค่าใช้จ่ายที่ข้าพเจ้าต้องรับผิดชอบ

หากมีข้อมูลเพิ่มเติมทั้งด้านประโยชน์และโทษที่เกี่ยวข้องกับการวิจัยนี้ ผู้วิจัยจะแจ้งให้ข้าพเจ้าทราบโดยรวดเร็วและไม่ปิดบัง

ข้อมูลส่วนตัวของข้าพเจ้าจะถูกเก็บรักษาไว้โดยไม่เปิดเผยต่อสาธารณะเป็นราย บุคคล แต่จะรายงานผลการวิจัยเป็นข้อมูลส่วนรวมโดยไม่สามารถระบุข้อมูลรายบุคคลได้ ข้อมูลของผู้เข้าร่วมการวิจัยเป็นรายบุคคลอาจมีคณะบุคคลบางกลุ่มเข้ามาตรวจสอบได้ เช่น ผู้ให้ทุนวิจัย สถาบัน หรือองค์กรของรัฐที่มีหน้าที่ตรวจสอบรวมถึงคณะกรรมการจริยธรรมการวิจัยในคน เป็นต้น

ข้าพเจ้ามีสิทธิ์ถอนตัวออกจากโครงการวิจัยเมื่อใดก็ได้ โดยไม่ต้องแจ้งให้ทราบล่วงหน้าหรือระบุเหตุผล และการไม่เข้าร่วมการวิจัยหรือถอนตัวออกจากโครงการวิจัยนี้ จะไม่มีผลกระทบต่อการบริการและการรักษาที่สมควรจะได้รับตามมาตรฐานแต่ประการใด

หากข้าพเจ้าได้รับการปฏิบัติที่ไม่ตรงตามที่ได้ระบุไว้ในเอกสารชี้แจงนี้ ข้าพเจ้าสามารถแจ้งให้ประธานคณะกรรมการจริยธรรมการวิจัยในคนทราบได้ที่ โรงพยาบาลหาดใหญ่ โทร. 074-273-100 ต่อ 1769

ข้าพเจ้าได้ทราบถึงสิทธิ์ที่ข้าพเจ้าจะได้รับข้อมูลเพิ่มเติมทั้งทางด้านประโยชน์และโทษจากการเข้าร่วมการวิจัย และสามารถถอนตัวหรืองดเข้าร่วมการวิจัยได้ทุกเมื่อ โดยจะไม่มีผลกระทบต่อการบริการและการรักษาพยาบาลที่ข้าพเจ้าจะได้รับต่อไปในอนาคต และยินยอมให้ผู้วิจัยใช้ข้อมูลส่วนตัวของข้าพเจ้าที่ได้รับจากการวิจัย แต่จะไม่เผยแพร่ต่อสาธารณะเป็นรายบุคคล โดยจะนำเสนอเป็นข้อมูลโดยรวมจากการวิจัยเท่านั้น

ข้าพเจ้าได้รับทราบข้อมูลของโครงการข้างต้น ตลอดจนข้อดี ข้อเสีย ที่จะได้รับจากการเข้าร่วมโครงการในครั้งนี้และข้าพเจ้ายินยอมที่จะเข้าร่วมในโครงการดังกล่าว จึงลงลายมือชื่อไว้

ลงชื่อ..... ผู้เข้าร่วมการวิจัย/วันที่.....
(.....)

ลงชื่อ.....ผู้ให้ข้อมูลและขอความยินยอม/หัวหน้าโครงการวิจัย/วันที่.....
(.....)

ในกรณีผู้เข้าร่วมการวิจัยอ่านหนังสือไม่ออก ผู้ที่อ่านข้อความทั้งหมดแทนผู้เข้าร่วมการวิจัยคือ .....

จึงได้ลงลายมือชื่อไว้เป็นพยาน

ลงชื่อ..... พยาน/วันที่.....
(.....)

BIOGRAPHY

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