การศึกษาเปรียบเทียบต้นทุนและประสิทธิภาพของการดูแลรักษาผู้ป่วยวัณโรค ระหว่างการใช้ระบบบริการสาธารณสุข ร่วมกับอาสาสมัครสาธารณสุข และ การใช้ระบบบริการสาธารณสุขร่วมกับ การสื่อสาร ด้วยโทรศัพท์มือถือ ภายใต้ระบบ DOTS-Plus ในเขตพื้นที่ภาคเหนือตอนบน

นางสาว ปิยะดา คุณาวรารักษ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตร์ดุษฎีบัณฑิต
สาขาวิชาวิจัยเพื่อการพัฒนาสุขภาพ (สหสาขาวิชา)
บัณฑิตวิทยาลัย จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2553

Cost Effectiveness : A Comparative Study Of Tuberculosis And Multi Drug Resistance Tuberculosis Case Management With Health Volunteer And Health Facility Base Model Versus Health Facility Base Plus Mobile Phone Communication By DOTS-Plus Strategy In Upper North Of Thailand

Miss Piyada Kunawararak

A Dissertation Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy Program in Research for Health Development
(Interdisciplinary Program)
Graduate School
Chulalongkorn University
Academic Year 2010

Thesis Title	Cost- Effectiveness: A Comparative Study Of Tuberculosis And Multi Drug Resistance Tuberculosis Case Management With Health Volunteer And Health Facility Base Model Versus Health Facility Base Plus Mobile Phone Communication By DOTS-Plus Strategy In Upper North of Thailand
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ปิยะดา คุณาวรารักษ์ : การศึกษาเปรียบเทียบต้นทุนและประสิทธิภาพของการดูแล รักษาผู้ป่วยวัณโรคระหว่างการใช้ระบบบริการสาธารณสุขร่วมกับอาสาสมัครและการใช้ระบบบริการสาธารณสุข ร่วมกับการสื่อสารด้วยโทรศัพท์มือถือ ภายใต้ระบบ DOTS-Plus ในเขตพื้นที่ภาคเหนือตอนบน.(COST-EFECTIVENESS : A COMPARATIVE STUDY OF TUBERCULOSIS AND MULTI DRUG RESISTANCE TUBERCULOSIS CASE MANAGEMENT WITH HEALTH VOLUNTEER AND HEALTH FACILITY BASE MODEL VERSUS HEALTH FACILITY BASE PLUS MOBILE PHONE COMMUNICATION BY DOTS-PLUS STRATEGY IN UPPER NORTH OF THAILAND) อ. ที่ปรึกษาวิทยานิพนธ์หลัก :รศ.ดร.สถิรกร พงษ์พานิช,อ. ที่ปรึกษาวิทยานิพนธ์ร่วม รศ.ดร พุทธกาล รัชธร,นพ. ดร.ธนรักษ์ ผลิพัฒน์, 121 หน้า.

หลักการและเหตุผล ประเทศไทยได้นำเอากลยุทธ DOTS มาใช้เพื่อเพิ่มประสิทธิภาพการควบคุมวัณโรค ตั้งแต่ ปี 2540 อย่างไรก็ตาม จนถึงปัจจุบัน ก็ยังไม่สามารถบรรลุเป้าหมายที่สำคัญตามตัวชี้วัดในการควบคุมวัณโรค ขององค์การอนามัยโลก

วัตถุประสงค์ เพื่อศึกษาเปรียบเทียบประสิทธิภาพของรูปแบบการดูแลรักษาผู้ป่วยวัณโรค ด้วยกลวิธี DOTS-Plus โดยการใช้ Mobile phone

วิธีการศึกษา การศึกษาทดลองแบบ open label,multi center Randomized controlled trial ในโรงพยาบาลของรัฐในเขตภาคเหนือตอนบน เพื่อเปรียบเทียบประสิทธิภาพของการดูแลรักษาผู้ป่วยวัณโรคทั้งกลุ่ม ดื้อยาและไม่ดื้อยา ระหว่างรูปแบบที่ 1 ใช้ระบบบริการสาธารณสุขร่วมกับอาสาสมัคร และรูปแบบที่ 2ใช้ระบบบริการสาธารณสุขร่วมกับการสื่อสารด้วยโทรศัพท์ มือถือ ในช่วง เมษายน 2551 ถึง เมษายน 2553 โดย มีขนาดตัวอย่าง ของกลุ่มที่ดื้อยา 19 ราย และ 30ราย ในกลุ่มที่ไม่ดื้อยา ติดตามการรักษาทุกรายจนครบ 18และ 6 เดือนจึงประเมินประสิทธิภาพ ของการดูแลรักษาทั้ง 2 รูปแบบ โดยเปรียบเทียบค่าใช้จ่ายทั้งหมด และค่าใช้จ่ายในการเพิ่มอัตราการรักษาสำเร็จ (CE Ratio) ของทั้งสองรูปแบบ

ผลการศึกษา ผลการรักษาของรูปแบบที่2 มีประสิทธิผลที่สูงกว่ารูปแบบที่1 อย่างมีนัยสำคัญทางสถิติ โดยที่รูปแบบที่2 มีอัตราการรักษาสำเร็จสูงถึงร้อยละ 100 ในกลุ่มที่ดื้อยา และไม่ดื้อยา ในขณะที่รูปแบบที่1 มีอัตรารักษาสำเร็จเพียงร้อยละ 73.7 ในกลุ่มที่ดื้อยา และร้อยละ 96.7 ในกลุ่มที่ไม่ดื้อยา (p=0.0001, 0.047) และพบว่าต้นทุนค่าใช้จ่ายในการดูแลรักษาผู้ป่วยวัณโรคทั้งกลุ่มดื้อยาและไม่ดื้อยาของรูปแบบที่2 ต่ำกว่าของรูปแบบที่ 1 โดยค่าใช้จ่ายที่สูงกว่ารูปแบบที่ 2 คือค่าใช้จ่ายในการตรวจด้านชัณสูตร ค่าขนส่งตัวอย่างและค่าตอบแทนอาสาสมัครโดยสูงถึง 4.6 เท่าของรูปแบบที่ 1 ในกลุ่มที่ดื้อยา และ เป็น 2 เท่าของรูปแบบที่1ในกลุ่มที่ไม่ดื้อยา และมีค่า CE ratio ที่ต่ำมาก คือ ลบ14.6 และลบ 5.0 ในกลุ่มที่ดื้อยาและไม่ดื้อยา

สรุป จากภาพรวมของการรักษาผู้ป่วยวัณโรคร่วมกับการสื่อสารด้วยโทรศัพท์เคลื่อนที่ภายใต้ระบบ DOTS-Plus พบว่าประสิทธิภาพของรูปแบบดังกล่าว มีความเป็นไปได้และให้ผลคุ้มค่าที่จะนำไปขยายต่อในพื้นที่ที่มีอัตราการดื้อยาวัณโรคหลายขนาน(MDR-TB) สูง

สาขาวิชา : วิจัยเพื่อพัฒนาสุขภาพ ลายมือชื่อนิสิต .....

ปีการศึกษา : 2553..... ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม.....

 # # 4989678220 : MAJOR RESEARCH FOR HEALTH DEVELOPMENT
KEYWORDS : DOTS-PLus / MDR-TB/ Cost effectiveness/ Mobile phone model/ Northern Thailand

PIYADA KUNAWARARAK : COST- EFFECTIVENESS ; A COMPARATIVE STUDY OF TUBERCULOSIS AND MULTI DRUG RESISTANCE TUBERCULOSIS CASE MANAGEMENT WITH HEALTH VOLUNTEER AND HEALTH FACILITY BASE MODEL VERSUS HEALTH FACILITY BASE PLUS MOBILE PHONE COMMUNICATION BY DOTS-PLUS STRATEGY IN UPPER NORTH OF THAILAND .

ADVISOR : ASSOCIATE PROFESSOR SATHIRAKORN PONGPANICH,Ph.D.
CO-ADVISOR : Associate Professor Buddhagarn Rutchatorn, Tanarak Plipat , M.D., Ph.D.,121 pp.

Backgrounds : Thailand has implemented of the Directly Observed Treatment Strategy to increase Tuberculosis control program efficacy but could not achieved key TB control program indicators as Indicated by WHO

Objectives : to compare the effectiveness of DOTS-plus strategy with mobile phone and DOTS-plus without mobile phone in upper north of Thailand

Methods : We conducted two TB control models with DOTS-plus strategy in MDR-TB and non MDR-TB group during April 2008 – April 2010 in upper-north Thailand as a control trial study. Model 1 was MDR- and non MDR-TB case management with health volunteer and health facility with DOTS-plus strategy.Model2 was MDR-TB and non MDR-TB case management with health facility with DOTS-plus strategy plus mobile phone. There were at least 19 patients in each arm of MDR-TB group and 30 patients in each arm of non MDR-TB group. We followed the patients 18 and 6 months for measuring the treatment outcomes.of MDR-TB and non MDR-TB group. And cost effectiveness was calculated as the average cost per patient treated successfully.

Results : The treatment outcome of Model 2 was effective than Model 2 with statistically significantly high success rate of 100% while Model 2 had success rate only 73.7% in MDR-TB group and also had high success rate of 100% while Model 1 had success rate in 96.7%.in non MDR-TB group ($p=0.0001$,$p=0.047$). And The total cost of managing a TB patient to treatment completion of model 2 was lower than Model 1 in both MDR-TB and non MDR-TB group. The higher cost was the cost of laboratory labor,volunteer payment and specimen transportation. It was high about 4.6 time of MDR-TB group and 2 time of non MDR-TB group.The CE ratio reflecting the cost benefits of both MDR-TB and non MDR-TB group in negative territory with CE ratio minus 14.6 in MDR-TB group and minus 5 in non MDR-TB group

Conclusions : In summary ,This paper describes our experiences with DOTS-Plus by mobile phone and the successful outcome suggests that DOTS-Plus by mobile phone is feasible ,affordable and cost effectiveness to extend application of process to area having high MDR TB rate

Field of Study : Research for Health Development
Academic Year : 2010

Student's Signature .....
Advisor's Signature .....
Co-advisor's Signature .....

ACKNOWLEDGMENTS

This study could be achieved because of collaboration from all hospitals in ChiangMai, Lumphun, Payao ChiangRai, Lumpang, Prae and Nan. I would like to also thank the doctors, nurses, pharmacists and laboratory technician who work in those hospitals for sending the specimens to the project regularly and cooperate well with the treatment schedules.

I would like to thank the Institutional Review Board and Ethics Committee of Chulalongkorn university and the Department of Disease Control for giving the project to roll out and would like to thank the Department of Disease Control and Chulalongkorn University for financial support to the project.

I am deeply appreciated the valuable advice for the doctors and nurses from Dr.Chareon Chuchottavone in order to properly taking care the patients in this study.

Finally, I would like to thank Associate Professor Dr. Sathirakorn Pongpanich,Dr.Tanarak Plipat , Assistant Professor Dr.Ratana Somrongthong and Associate Professor Dr. Buddhagan Rutchatorn for their great support and advice.

I would like to thank the above mentioned persons again on this occasion Goodness of this study if any should be used to praise my father,my mother,my teachers as well as my beloved institute.

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CHAPTER 1

Introduction

Rational and Background

Tuberculosis became an important re-emerging infectious disease since AIDS epidemic. WHO reported that 1/3 of the world population is infected with the bacteria. Among these, 16-20 millions are active cases. It is estimated that there are 8 millions new tuberculosis cases per year and causes 2 millions deaths which took place mostly in developing countries. Due to above mention figures, WHO declared Tuberculosis an emergency disease which need immediate intervention to solve the problem.[1]

In the year 2006 WHO reported that Thailand is among the highest TB burden countries in the world. The current estimates for the prevalence and incidence of TB is based on a prevalence survey conducted in 1991, recent limited prevalence surveys and routine case notifications. Additional surveys are planned to obtain better estimates of disease burden including among people living with HIV/AIDS during the next two years and beyond. Routine programme surveillance is also being strengthened with further improvements in the electronic and reporting system already in place in the country. In 2006, the NTP adopted the quarterly reporting system replacing the thrice-yearly reporting system.This will make international comparisons more straightforward as well as facilitate aligning to reporting cycles of major donors including the Global Fund.

Thailand is reporting generalized HIV epidemic. Nationwide surveillance for TB/HIV co-morbidity is routinely undertaken. The HIV epidemic has had a significant impact on TB with higher case notifications among young adult.Since AIDS spread to Thailand in 1984, reported Tuberculosis cases also increased steadily to 58,670 cases in 2005.[2] Among these, 30,101 were new smear positive cases, 1,784 were relapse cases, 19,159 were new smear negative cases, and 7,626 were extra-pulmonary Tuberculosis. There have been 301,046 symptomatic HIV and AIDS reported cases in Thailand till 2005 with 84,437 cases (25.5%) also suffered from Tuberculosis.

Multi-drug resistant tuberculosis in Thailand have been regarded as the third epidemic and become global emergency since 1993. The multi-drug resistant TB is at least resistant to 2 drugs which are isoniazid and rifampicin. The MDR-TB is uncured despite its rare occurrence. A major cause of MDR-TB is either irregular drug taking or not completing course of drug taking. In 1997, the WHO reported Thailand's MDR-TB at around 3000 cases considered as high tendency. By December 1998, the rate of drug resistant TB was 26%, 13% to isoniazid, 12% to streptomycin, 7% to rifampicin, 7% to ethambutol and 3% to multi-drugs. Compared between 1968 and 1998, the percentages of drug resistant TB had increased for each drug. Factors related to drug resistant TB were number of lesions in lungs, family history of TB and HIV positive history while factors related to MDR-TB were history of TB treatment, TB family history (review by Dr. Petcharawan)

Northern Thailand has been hardest hit from AIDS compared to other parts of the country and contributed 30% [3] of reported cases. The AIDS epidemic in the area caused high burden of Tuberculosis cases and un-achieved related indicators. Data from Tuberculosis Center Region 10 showed that death rate were 11-24% (target 9%), cure rate 65-77% (target 85%), default rate 1.6-12.5% (target 5%), and relapse > 10%.and the important data that should be a cause of low success rate is the high rate of NTM.[56]The factors related to death among TB patients included HIV co-infection, had other co-morbidity especially DM HT and COPD, and late diagnosis.

Proportion of Multi drugs resistance TB (MDR-TB) in the region has been increased both primary drug resistance and acquired drug resistance. Studies from Tuberculosis Center Region 10 showed 4 % MDR-TB among never-before-treated TB patients while a study from Chiang Rai by Yashiyama found MDR-TB as high as 6 %.[5] It was higher than Hot spot point (3%) of WHO criteria.[4]There has no active strategy to cope with MDR-TB problem up until recently due to lack of laboratory capacities. However, the laboratory facilities of the center is improved and be able to perform DST and get result within one month. Tuberculosis Center Region 10 is now ready to implement DOTS-Plus strategy recommended by WHO.

The Directly Observed Treatment Short-course (DOTS) strategy of the World Health Organization (WHO) aims to reduce initial drug resistance and acquired drug resistance. The main strategy is that patient has to swallow the medications in front of his or her supervisor which could be family member, health care personnel, volunteer, or community member. There are five elements in DOTS: political commitment ; case detection using sputum microscopy ; standard short-course chemotherapy under proper case management; direct observation of treatment; and a standard recording and reporting system. Thailand adopted DOTS strategy and used for TB patients in 1996 [9] and later expand to cover all area of the country. DOTS is now widely accepted from health personnel. Future plan is to distribute responsibility to local authority through primary care unit.

DOTS-Plus is another add-on strategy to tackle MDR-TB and focusing on sputum culture, drug sensitivity test, availability of 2nd line drug. DOTS-Plus is not intended as a universal strategy, and is not required in all settings.[10] DOTS-Plus should be implemented only in selected areas with moderate to high levels of MDR-TB. DOTS-Plus is being implemented in Bolivia, Costa Rica, Estonia, Haiti, Karakalpakstan (Uzbekistan), Latvia, Malawi, Mexico, Peru, Philippines and the Russian Federation (Arkhangelsk, Ivanono, Tomsk and Orel Oblasts). More recently, DOTS-Plus projects have also been approved in Georgia, Honduras, Jordan, Kenya, Kyrgyzstan, Lebanon, Nepal, Nicaragua, Romania and Syria. [12] The elements of DOTS-plus include the followings.[8]

1. Political commitment is of utmost importance in treatment of tuberculosis in general ,and MDR-TB specifically. For DOTS-Plus it is necessary to obtain the support of the local authorities, because first of all, financing is necessary in order to set up this project. Secondly, government should regulate the distribution of tuberculosis drugs. Patients should not be allowed to buy them in drugstores, because if self-administered, it can be done inappropriately, thus creating more resistant strains of Mycobacteria tuberculosis.

2. Coordination of all parties involved in DOTS-Plus project is necessary. At the community level, former patients can be recruited to help current patients.Social

workers must be taught how to deal with MDR-TB patients. The DOTS-Plus project should be integrated with an existing DOTS project and with the National Tuberculosis Program. On the international level, there must be collaborative projects.

3. Laboratory aspects include culture identification of Mycobacterium tuberculosis and providing drug susceptibility tests to first and second line drugs. Ensure high quality of work.

4. Treatment strategy The doctors should use treatment strategy where by ascertain that the patients actually take the drugs given to them . For two years the patients must either receive drugs in a hospital or at a local medical center. The doctors should know what kind of side effects to expect and how to deal with them.

5. Information systems and data management A well functioning DOTS-Plus program has to have efficient information systems in order to allow the tracking of treatment of each individual and usage of data in the research of the disease.

In terms of medication treatment used in DOTS-Plus strategy, there are 2 acceptable standard formats.[7]

1. Empirical treatment: In MDR-TB patients with severe symptoms or positive sputum exam at the end of 2nd month of treatment. The patient will get standard CAT 1 or CAT 2 regimen with at least 4 medications plus Kanamycin injection under background DOTS strategy. This treatment format uses population DST results from that geographical area as information to help decide on how to treat the patient.

2. Individual treatment: In patients who had DST result at the beginning of the treatment, the medications used will be according to individual DST result following guideline for the programmatic management of drug resistance tuberculosis (table 1)

TABLE 1 Individualized regimen design based on DST for first-line drugs

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN (DAILY UNLESSOTHERWISE STATED)	COMMENTS
H-R	*Z-E-injectable agent-fluoroquinolone (± one or two Group 4 agents)*	One Group 4 agent is sufficient if E and Ze susceptibility has been ascertained. Two Group 4 agents should be used in extensive disease, or if the DST result is questionable (i.e reported susceptibility to E or Z despite a history of these agents being used in a failing regimen).
H-R (± S) and E or Z	*Z or E*-injectable agent-fluoroquino-lone (+ two or more Group 4 agents)	Only use the first-line agents to which the patient's strain is susceptible. Use alternative injectable agent if S resistance is present. More than two Group 4 agents should be used in extensive disease or if resistance to E and Z is present or suspect-ed. Group 5 agents can be considered if an adequate regimen of four drugs cannot be formed based on DST.

H = *isoniazid;* R = *rifampicin*; E = *ethambutol;* Z = *pyrazinamide;* S = *streptomycin*

The basis is to use 3 new medications plus Kanamycin injection for 3-6 months. The overall treatment course should be 18 months long. The laboratory follow up should be as the followings: BUN, Creatinine, and LFT every 3 month, Chest X-ray every 6 month.

Table 2 Recommended treatment regimens for new smear positive and DST shows drug-susceptible disease

TB treatment regimens	
Initial phase	Continuation phase
2HRZE(S)	*4HR*

The investigator, together with TB center region 10 staff, has evaluated the facilities and health service as well as community network in upper northern Thailand and concluded that it is possible to introduce DOTS-Plus strategy in the area. The laboratory (element #3) will be novel for the region. We hope that this initiative will help improve the overall efficacy of TB treatment in the area.

However according to several reports, DOTS-Plus strategy has not been so successful. Tuberculosis center Chennai India summarized treatment of MDR-TB TRC experience between 1980 – 2005 showed that cure rate was at only 65%.[12] Drug resistance is often attributed to a patient's noncompliance with the therapeutic regimen. Noncompliance, [11] however, has/many cause such as poverty, lack of scientific awareness about the disease, homelessness, side effects of the anti-TB drugs, and especially social stigma. This findings underscore the importance of understand local needs and socio-culture aspects of community to implement TB control program effectively.

Mobile phone becomes essential part of daily life activities for most Thai people nowadays. It has potential in helping health care personnel communicate with TB patients since it is convenience and confidential and offers protection against social stigma[13]. Vitsarutratana et al. reported encouraging evidences using mobile phone to follow-up TB patients in 2 districts of Chiang Mai province. They found that this strategy increased cure rate and improved patients' psychological status. Most patients felt warm, less social stigma, more willingness to taking care of themselves through mobile phone talks with health personnel.

The investigator hopes that using DOTS-Plus following WHO guideline by introducing new laboratory techniques (identify for NTM, DST) together with using mobile phone to communicate with the patients will help improve patients' compliance to treatment and at the same time raises patient's understanding on their co-morbidities (DM, HT, and CVD) if any resulting in more effective overall TB control in the region.

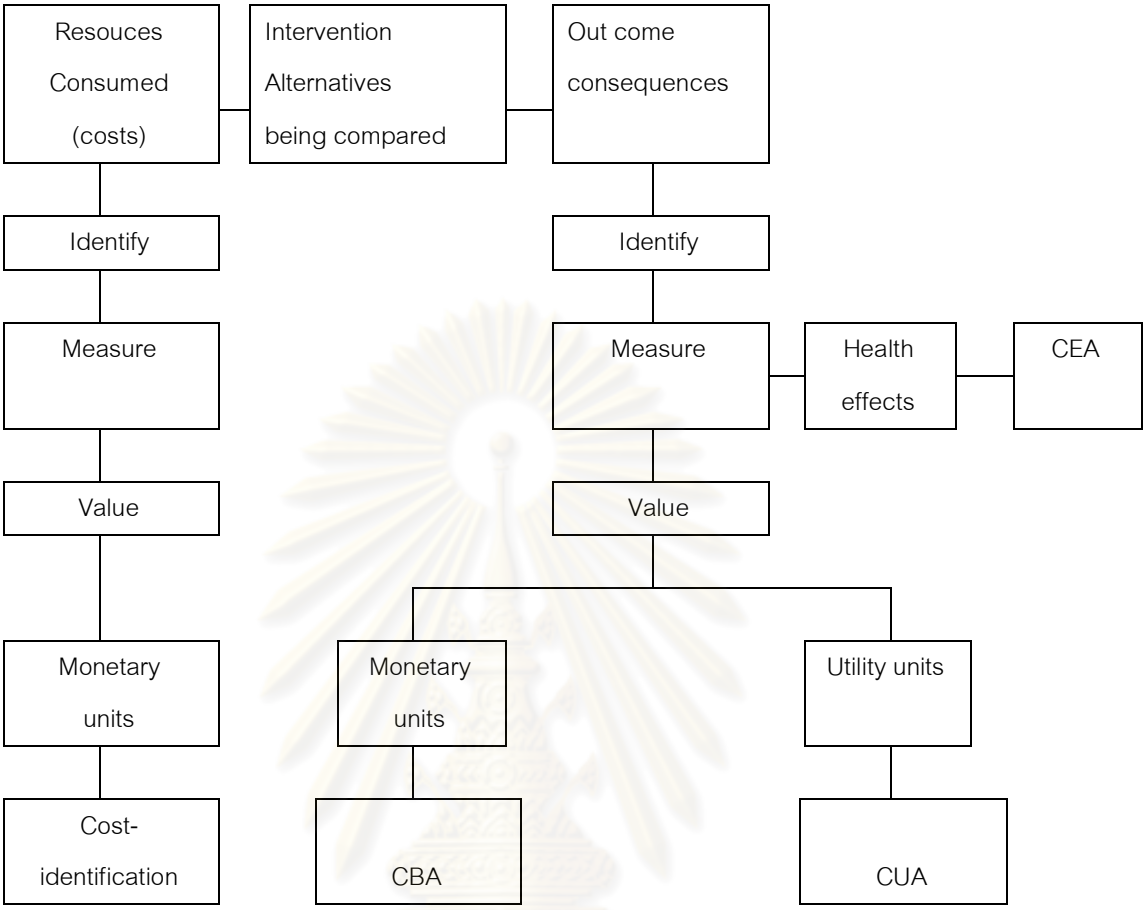
Conceptual Framework

The DOTS Plus Framework for the Management of TB and Multi-Drug-Resistant TB

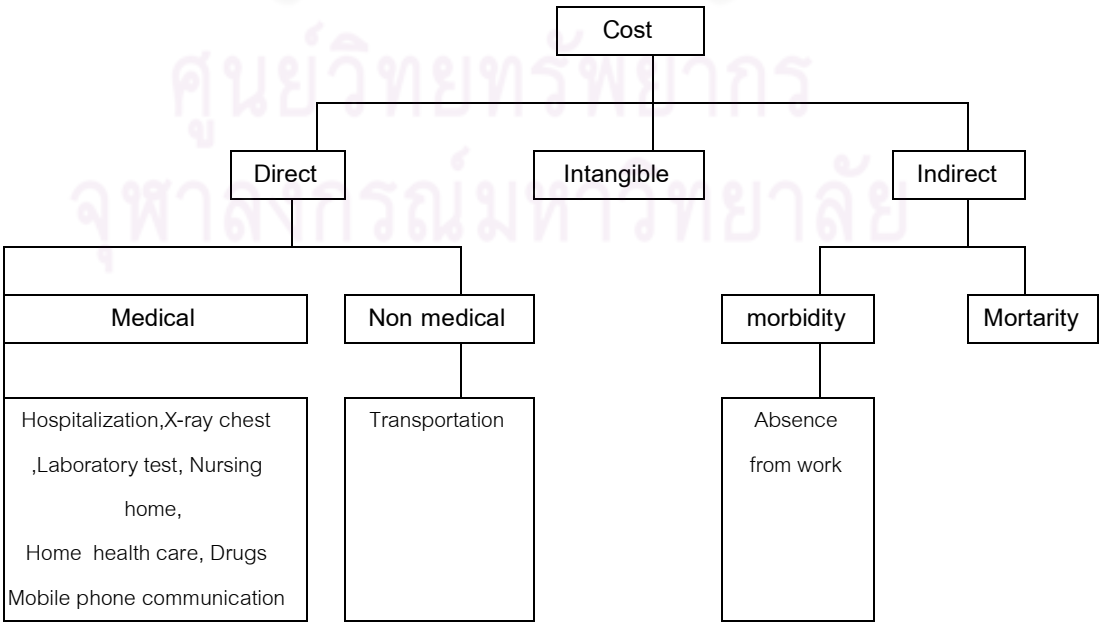
The framework is organized around the same five components of the DOTS strategy, as the underlying principles are the same. The core components are comprehensive ensuring that all essential elements of the DOTS Plus strategy are included and we compared the framework between DOTS and DOTS-Plus as follows:

DOTS	DOTS Plus
1. Political commitment	1.Sustained political and administrative commitment 1.1 A well-functioning DOTS program. 1.2 Long-term investment of staff and resources. 1.3 Coordination efforts between the community, Local governments, and international agencies
2. Case detection using sputum microscropy	2. Diagnosis of MDR TB through quality-assured culture and drug susceptibility testing. 21.Proper triage of patients into DST testing and. the DOTS-Plus program
3.Standard short-course chemotherapy under Proper case management.	3.Appropriate treatment strategies that utilize secondline drugs under proper management conditions 3.1 Rational treatment design (evidence-based.) . 3.2 Directly observed therapy (DOT) ensuring long-term adherence. 3.3 Monitoring and management of adverse drug Reactions
4. Direct observation of treatment	4.Uninterrupted supply of quality-assured anti-TB drugs
5. Standard recording and reporting system	5.Recording and reporting system designed for the DOTS Plus programs that enable performance monitoring and evaluation of treatment outcome.

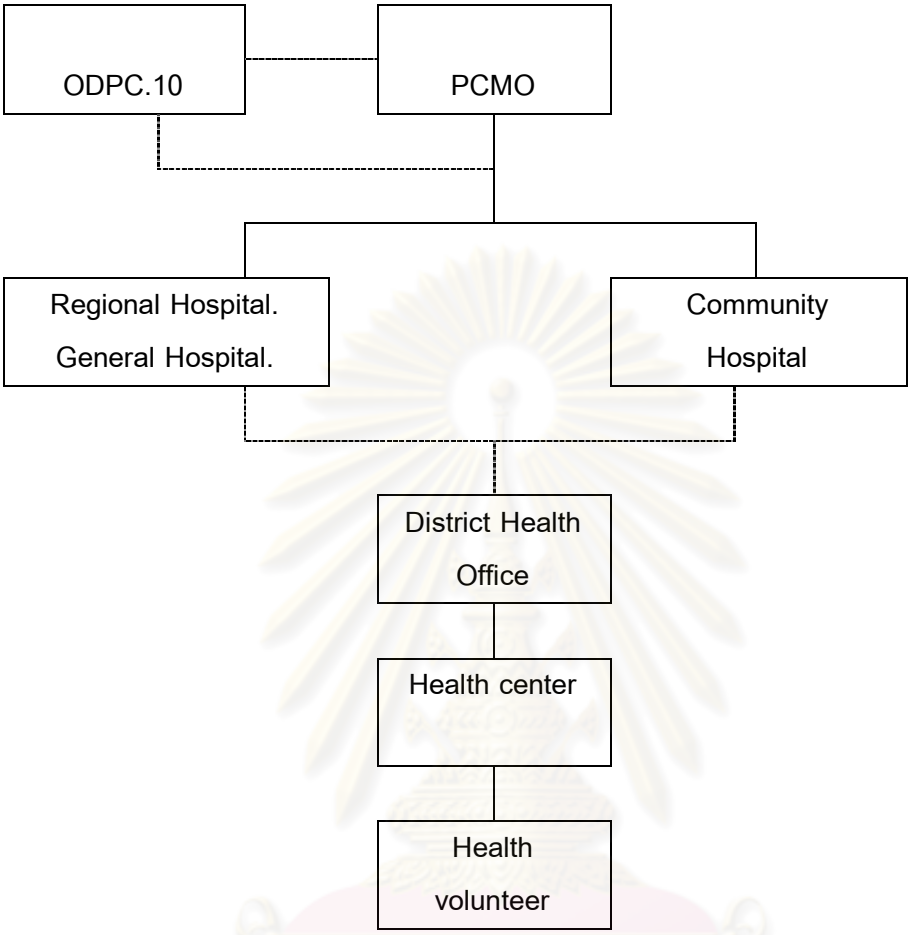
Figure 1 Frame work of Cost analysis



*** Cost benefit analysis and Cost Utility analysis are not include**



Health Facility



Research Question

Dose adding communication via mobile phone on top of DOTS-Plus for non MDR-TB patient improves the TB treatment outcomes.

Research Objective

To conduct comparative study on TB control effective model in northern area

1.Primary Objective

1.1 To compare the effectiveness of TB treatment outcomes between non MDR-TB patients who got routine DOTS-plus care model and patients who got routine DOTS-plus care model plus mobile phone communication.

1.2 To compare the effectiveness of TB treatment outcomes between MDR-TB patients who got routine DOTS-Plus care model and patients who got routine DOTS-Plus care model plus mobile phone communication.

2. Secondary Objective

2.1 To compare cost effectiveness of TB treatment outcomes between non MDR-TB patients who got routine DOTS-plus care model and patients who got routine DOTS-plus mobile phone communication.

2.2 To compare cost effectiveness of TB treatment outcomes between MDR-TB patients who got routine DOTS-Plus care model and patients who got routine DOTS-Plus care model plus mobile phone communication.

Research Hypothesis

Ho : DOTS-plus communication among non MDR-TB patients using mobile phone will be more effective than conventional Health facility

Ho : DOTS-plus communication among MDR-TB patients using mobile phone will be more effective than conventional Health facility

Ethical Considerations

Ethical approval was obtained from the Ethical Review Committee for Research Involving Human Research of Chulalongkorn University and the Ethical Review Committee for Research in Human Subjects , Department of Disease Control.

All participants will be given adequate information, and written informed consent will be obtained from each participant. Participants may withdraw from the study at any time without effect to their care and treatment.

All collected information will be kept confidential and be used only by investigators and health staff. Result will be distributed in collective manner not in individual. Each patient will be taking care of by the same health staff team through out the study period.

Expectation benefit

Short-Terms Benefit

1.1 Help to decrease rate of epidemic of drug resistance against tuberculosis in various kinds (MDR-TB)

1.2 Help to increase cure rate of tuberculosis control plan in the area of zone 1

1.3 To decrease death rate of the patient of tuberculosis

Government (For Ministry of Public Health)

If rate of drug resistance in various kinds is decreased, the government could save cost for the patient resisting various kinds of drug so much. Then, the budget for such cost can be spent to develop quality of life of the patient in other necessary issues.

Tecnology Support Sector (Department of Disease Control)

This will help the body supporting academic matter to be guided for developing system of caring the tuberculosis patient both who resists the drug or does not resist the drug against tuberculosis, including the tuberculosis patient having complicacy of diabetes, high blood pressure, and heart and coronary artery disease efficiently. This also help the body charged to study to has database to study development of caring health of the patient having several diseases

Service Sector

This can help the body providing service in public health matter has time to service the patient with high quality due to the efficient system to care of the patient.

Limitations

Cost-effectiveness calculation in terms of economy is difficult . This study did not include the capital cost and the cost was integrated by project.

Table 3 Administration & Time Schedule

Time / Phase	Year 2008				year 2009			
	Month 1-3	Month 4-6	Month 7-9	Month 10-12	Month 13-15	Month 16-18	Month 19-21	Month 22-24
1.Prepare Proposal by	x							
2. Complete literature review by	x			x				x
3.Complete field work by								
3.1 screening MTB pt with PCR test		X	X	X	X	X	X	X
3.2 Culture MTB pt								
3.3 Drug sensitivity test								
3.4 direct smear for AFB	X	X	X	X	X	X		
3.5 sputum Culture	X	X	X	X	X	X		
3.6 Drug sensitivity test when culture positive								
3.7 Chest X-ray	X	X		X		X		
3.8 Blood Chemistry	X	X		X		X		
3.9 blood for sugar test								
3.10 home visit by volunteer in non mobile group	X	X	X	X	X	X		
3.11 Telephone call every day for mobile phone group	X	X	X	X	X	X		
3.12 Conference meeting with TB staff of government hospital in 7 provinces , upper north Thailand	X		X					
3.13 supervision	X		X		X			
4. complete analysis by								x
5. Give presentation on								x
6. Complete final report by								x

Operation definition

The following of variable state in the purpose of the study were definded as :-

MDR-TB [55] : A patient who has active tuberculosis with bacilli resistance at lease to both isoniazid and rifampicin

Non MDR-TB [55] : A patient who have culture positive and drug susceptibility shows drug-susceptible disease

DOTS [55] : is a strategy used to reduce the number of tuberculosis cases. In DOTs,healthcare workers observe patients as they take their medicine. Left alone,many people with tuberculosis fail to take all their medication and contribute

to the spread of drug-resistance tuberculosis. .And DOTS strategy was introduced to 5 components : 1) Sustained political commitment 2) Access to quality-assured sputum microscopy. 3) Standardized short-course chemotherapy for all cased of TB under proper case management conditions, including direct observation of treatment. 4) Uninterrupted supply of quality-assured drugs. 5) Recording and reporting system enabling outcome assessment of all patients and assessment of overall programme performance.

DOTS-plus [55]: is a comprehensive management strategy under development and testing that includes the five tenets of the DOTS strategy. DOTS-plus takes into account specific issues (such as the use of second-line anti-TB drugs) that need tobe addressed in area where there is high prevalence of MDR-TB.

Treatment outcomes [55]: mean that at the end of the treatment course for each patient with sputum positive should be show the result of 6 criteria as below :

1 Cured : A patient who was initially smear-positive and who was smear-negative in the last month of treatment and on at least one previous occasion.

2 Completed treatment : A patient who had completed treatment duration but did not meet the criteria for cure of failure.

3. Died : A patient who died from any cause during treatment.

4. Treatment failure : A patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment.

5.Defaulted : A patient whose treatment was interrupted for 2 consecutive months or more.

6. Transfer out : A patient who transferred to another reporting unit and for whom the treatment outcome is not known.

7 Successfully treated : A patient who was cured or who completed treatment.

Abbreviations

AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
CP	Continuous Phase
DOT	Directly observed treatment
DOTS	The internationally recommended strategy for TB control
DST	Drug susceptibility testing
DTC	District TB Coordinator
DM	Diabetis Melitus
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
HIV	Human immunodeficiency virus
HT	Hypertension
ICMR	Indian Counsil of Medical Research
IP	Intensive Phase
IRL	Intermediate reference Laboratory
LFT	Liver function test
MDR	Multidrug resistance (resistance to isoniazid and rifampicin)
MDR-TB	Multidrug-resistant tuberculosis
NCCLS	The National Committee for Clinical Laboratory Standards
NTM	Non TuberculosisMycobacterium
NTP	National tuberculosis control programme or equivalent
RNTCP	Revized National Tuberculosis Control Program
RR	Relative Risk
STR	Standardized treatment regimen
TB	Tuberculosis
WHO	World Health Organization
ODPC.10	Office of Disease Prevention and Control 10
PCMO	Provincial Chief Medical Office
DTC	District Tuberculosis coordinator
NHSO	National Health Seculity Organization
TAD	Treat after default
VMI	Vendor Managed Inventory

CHAPTER 2

Review of Literature

Gagandeep Singh Grover and Jaspreet Takkar[57] had reviewed the recent advances in Multi-drug resistant Tuberculosis in the year 2008 as follow :-

Tuberculosis (TB) persists as a global public health problem of serious magnitude requiring urgent attention. Current global efforts to control TB have three distinct but overlapping dimensions: humanitarian, public health, and economic.

Alleviating illness, suffering, and death of individuals due to TB is the major humanitarian concern for a patient-centered approach to TB control. The public health dimension concerns proper diagnosis and treatment of patients with TB to decrease disease transmission. This necessitates the development of well-organized TB control programs (responsive and adaptable to the reforming health sector). TB is responsible for considerable direct and indirect costs to the individuals and the society. The economic dimension of TB control relates to a reduction of these costs, alleviation of poverty, and promotion of development.[14]

The emergence of resistance to drugs used to treat TB, and particularly multi-drug-resistant TB (MDR TB), has become a significant public health problem and an obstacle to effective TB control.[15]

Drug resistance is manifested when there is a selective growth of resistant mutants among the actively multiplying bacillary population in the presence of drugs. The emergence of drug resistance depends upon the frequency of drug resistant mutants in the susceptible bacillary population, the size of the actively multiplying bacillary population in the lesions, and the anti-microbial quality of the drugs used. Drug resistance of the Mycobacterium tuberculosis isolated from patients who have been treated for 1 month or more is defined as “acquired drug resistance“, while that of patients who have never been treated previously or treated for less than 1 month is called —primary drug resistance“.[16]

Resistance to a single drug is defined as “mono resistance“ and resistance to two or more drugs is defined as “poly resistance.“ Resistance to at least Isoniazid and

Rifampicin is termed as “MDR“.

Extent of the Problem

In a study among 50,000 TB cases in 35 countries, the World Health Organization (WHO), Centers for Disease Control (CDC), and International Union Against Tuberculosis and Lung Diseases found that in India, Russia, Latvia, Estonia, The Dominican Republic, Argentina, and the Ivory Coast (the so called “Hot Zone“), TB was resistant to the commonly prescribed drugs Isoniazid and Rifampicin. One third of the countries surveyed had a MDR TB level between 2-14%.[17] In another study among 64,104 TB cases from 58 geographical settings, WHO found drug resistant TB to be between 2.9% to 40.8%. The prevalence of drug resistance was directly related to the proportion of previously treated cases registered and inversely related to the proportion of TB cases treated under directly observed treatment short course (DOTS)[18] A study conducted by the Indian Council of Medical Research (ICMR) in India in nine centers found MDR TB ranging from 0.6% to 3.2% in respect to initial drug resistance and 6% to 30% in respect to acquired drug resistance.[19] High proportions of drug resistance have been found in Wardha, New Delhi, and Tamil Nadu. Drug resistance to Isoniazid was 20.9%, 50.7%, and 23.6% respectively while MDR TB was 9.6%, 33.7%, and 23.3%, respectively.[20] Drug resistant TB has frequently been encountered in India and its prevalence has been known virtually from the time anti-TB drugs were introduced. However, there is no state-representated surveillance data of drug resistance among patients with TB and a major limiting factor in conducting drug resistance studies is the lack of state level Quality Assured Culture and Drug Sensitivity (DST) laboratory facilities. Tuberculosis Research Center and National Tuberculosis Institute have found MDR TB levels of less than 1% to 3% in new cases and 12% in re-treatment cases. With a rapid increase in coverage of Revised National Tuberculosis Control Programme (RNTCP) and a high cure rate observed in most regions, low emergence of drug resistance is expected across the country.[15]

Causes of Resistance

Drug-resistant TB has microbial, clinical, and programmatic causes. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows drug resistant mutants to become the dominant strain in a patient infected with TB.[15]

Transmission of Drug-Resistant TB

Drug-resistant and drug-susceptible TB is transmitted in the same way. For many years, drug-resistant TB was believed to be less infectious than drug-susceptible TB. This belief was largely based on animal studies. Now, it has been found that drug-resistant bacilli were not less infectious; in fact, contact with previously untreated patients had a similar risk of infection, regardless of whether the bacilli were drug susceptible or drug resistant.

However, an increased risk of infection has been found to occur when in contact with a patient with drug-resistant TB who had been previously treated and this increased risk resulted from prolonged exposure rather than increased infectiousness of the drug-resistant bacilli.[21]

Prevention of MDR TB

The key to the successful prevention of the emergence of drug resistance is adequate case finding, prompt and correct diagnosis, and effective treatment of infected patients. This can be achieved through the use of DOTS.[22]

Drug Resistance A new protocol for state-wide Drug Resistance Surveillance (DRS) under RNTCP was developed in 2005. Over the next five years, RNTCP plans to systematically carry out state-wide DRS surveys in the states of Andhra Pradesh, Delhi, Gujarat, Kerala, Maharashtra, Orissa, Uttar Pradesh, and West Bengal. Besides this, the ICMR will be conducting a separate DRS in the states of Tamil Nadu and Sikkim.[23]

DOTS Plus

DOTS Plus refers to a DOTS program that adds components for MDR TB diagnosis, management, and treatment. TheWHO-endorsed DOTS Plus program

began in 2000. At that time, the Green Light Committee (GLC) was established to promote access to high quality second line drugs for appropriate use in TB control programs. In 2002, the Global Fund to fight AIDS, TB, and Malaria (GFATM) started financing TB control programs, including MDR TB, greatly reducing the economic barrier to MDR TB control. DOTS-Plus programs can and should strengthen the basic

DOTS strategy.[15]

The RNTCP views the treatment of MDR TB patients as a "standard of care' issue. Recognizing that the treatment of MDR TB cases is very complex, treatment will follow the internationally recommended DOTS Plus guidelines and will be done in designated RNTCP DOTS Plus sites. There will be at least one site in each state that will have ready access to an RNTCP-accredited culture and drug susceptibility testing (DST) laboratory.[23]

The DOTS Plus Framework for the Management of Multi-Drug-Resistant TB

The framework is organized around the same five components of the DOTS strategy, as the underlying principles are the same. The core components are comprehensive ensuring that all essential elements of the DOTS Plus strategy are included and are as follows:

1.Sustained political and administrative commitment. Œ

1.1 A well-functioning DOTS program.

1.2 Long-term investment of staff and resources.

1.3Coordination efforts between the community, local governments, and international agencies.

2. Diagnosis of MDR TB through quality-assured culture and drug susceptibility testing.

21.Proper triage of patients into DST testing and the DOTS-Plus program.

3. Appropriate treatment strategies that utilize secondline drugs under proper management conditions.

- Rational treatment design (evidence-based.)
- Directly observed therapy (DOT) ensuring long-term adherence.
- Monitoring and management of adverse drug reactions.

4.Uninterrupted supply of quality-assured anti-TB drugs.

5.Recording and reporting system designed for the DOTS Plus programs that enable performance monitoring and evaluation of treatment outcome.

Each of these components involves more complex and costly operations than those for controlling drug-sensitive TB. However, addressing multi-drug resistant TB will strengthen the existing TB control program.

Case finding strategy At present, RNTCP does not have sufficient quality-assured laboratory capacity to do DST in all patients. Hence, the program will use a strategy that enrolls patients with a very high-risk of MDR TB into RNTCP DOTS Plus activities and treatment with the RNTCP Category IV regimen. Patients who are defined as an MDR TB suspect should be identified and investigated further for MDR TB. A MDR TB Suspect is defined as a Category II patient who is smear positive at the end of the fourth month of treatment or later.

Drug-resistant cases A patient is confirmed to have multi-drug-resistant TB only by an RNTCP quality assured intermediate reference laboratory (IRL). Such patients are classified according to the following definition. A confirmed MDR TB case is an MDR TB suspect who is sputum culture positive and whose TB is due to bacilli that are resistant in-vitro to at least isoniazid and rifampicin (the DST result being from an RNTCP accredited IRL).

Bacteriology With respect to drug-resistant TB, bacteriology includes both sputum smear microscopy and culture examination. Smear microscopy and culture should be performed and results reported according to international standards.

Smear and culture conversion Two separate indicators, one based on sputum smears and the other on cultures should be calculated. Patients will be considered culture converted after having two consecutive negative cultures taken at least one month apart.

Treatment of Multi-Drug-Resistant Tuberculosis Classes of anti-TB drugs The classes of anti-TB drugs have traditionally been divided into first- and second-line drugs with isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin being the primary first-line drugs. These drugs can also be grouped based on efficacy, experience of use, and drug class. The different groups are shown in Table 4.

Table 4: Anti TB Drugs

Grouping	Drugs
Group 1: First line anti TB drugs	*Isoniazid (H),Rifampicin(R),Ethambutol (E),Pyrazinamide (Z)*
Group2: Injectable anti TB drugs	*Streptomycin (S),Amikacin (Am), Kanamycin (Km), Capreomycin (Cm),*
Group3:Fluoroquinolones	*Ciprofoxacin (Cfx); Ofoxacin (Ofx); Levofoxacin (Lvx); Moxifoxacin (Mfx); Gatif oxacin (Gfx)*
Group4:Oral second-line anti-TB drugs	*Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizadone (Trd); para-aminosalycilic acid (PAS); Thiacetazone (T)*

Category IV regimen

RNTCP will be using a standardized treatment regimen for the treatment of MDR-TB cases under the program: the Intensive Phase will consist of 6-9 months of *Km, Ofx, Eto, Cs, Z,* and *E* and the Continuation Phase will consist of 18 months of *Ofx, Eto, Cs,* and *E.*

The RNTCP will be using a standardized treatment regimen (STR), comprising of 6 drugs (*kanamycin, ofoxacin, ethionamide, pyrazinamide, ethambutol, and cycloserine*) during 6-9 months of the Intensive Phase and 4 drugs (*ofoxacin, ethionamide, ethambutol, and cycloserine*) during the 18 months of the Continuation Phase. p-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any of the bactericidal drugs *(K, Ofx, Z, and Eto)* or any 2 bacteriostatic drugs (*E* and *Cs*) are not tolerated.

Drug dosages and administration

Drug dosages for MDR TB cases are decided according to the weight band recommendations given in Table 5.

Table 5: Recommended dosage according to weight in DOTS Plus

Drugs	< 45 Kg	> 45 Kg
Kanamycin	500 mg	750 mg
Ofoxacin	600 mg	800 mg
Ethionamide	500 mg	750 mg
Ethambutol	800 mg	1000 mg
Pyrazinamide	1250 mg	1500 mg
Cycloserine	500 mg	750 mg
Na PAS	10 mg	12 mg

All drugs should be given in a single daily dosage under directly observed treatment (DOT) by a DOT provider. Pyridoxine at a dose of 100mgs should be administered to all patients on an RNTCP Category IV regimen.

If a patient gains weight during treatment and crosses the weight-bands range, the DOTS Plus site committee may consider moving the patient to the higher weight-band drug dosages. The new higher dosages are provided whenever the patient is due for the next supply of drugs in the normal course of treatment and not as soon as change of weight is noted as shown in Table 3. In deciding about the dosages, apart from the considerations mentioned above, it is also necessary to rule out the existence of medical illnesses or organ dysfunctions in the individual by conducting routine

Table 6 : Drug formulation and packaging in DOTS Plus

Drugs	<45 Kg	45Kg
Kanamycin	0.5 g vial	0.75 g vial
Ofoxacin	200 mg tablets (3)	400 mg tablets (4)
Ethionamide	250 mg tablets (2)	250 mg tablets (3)
Ethambutol	800 mg tablet (1)	1000 mg tablet (1)
Pyrazinamide	500 mg tablet (1) + 750 mg tablet (1)	750 mg tablet (2)
Cycloserine	250 mg tablets (2)	250 mg tablets (3)
Na PAS	100 g box	100 g box

hematological investigations like full blood count, random blood sugar, liver and kidney function tests, etc., and urine microscopy. Other investigations like skiagram, ultrasound etc. may be appropriately carried out as required in a particular case.

Treatment duration

The recommended duration of administration of the intensive phase (IP) is guided by smear and culture conversion. The minimal recommendation is that the IP should be given for at least 6 months. After 6 months of treatment, the patient will be reviewed and the treatment changed to the CP if the culture results from the 4th month are negative. If the culture results from the 4th month remain positive, the DOTS-Plus site Committee will decide on extending the IP treatment by up to 3 months. If the 4th month culture is still awaited after 6 months of treatment, the IP will be extended until the result is available, with further treatment being decided on according to the culture result when this becomes available. After a maximum of 9 months of IP treatment, the patient will be initiated on the CP of treatment. The recommended duration for CP is 18 months.

For follow-up culture and DST, the patient needs to go to DTC. After discharge, the patient will visit the DOTS-Plus site facility only if deciding to change from the IP to the CP, at the end of treatment, at the time of the management of adverse reactions, and at the time of change of treatment due to non-response.

Management of Contacts of MDR TB

Among contacts of patients with MDR TB, the use of isoniazid may reasonably be questioned. Close contacts of MDR TB patients should receive careful clinical follow-up for a period of at least 2 years. During this stage, no prophylactic treatment of MDR TB contacts is recommended over and above the existing RNTCP guidelines. The following measures should be taken to prevent the spread of MDR TB:

- Early diagnosis and appropriate treatment of MDR TB cases
- Screening of contacts as per RNTCP guidelines and follow-up for 2 years
- Further research into effective and non-toxic chemoprophylaxis in the areas of high MDR-TB prevalence.[21-27]

Conclusion

DOTS is a proven cost-effective TB treatment strategy. A combination of technical and managerial components, DOTS quickly makes infectious cases non-infectious and breaks the cycle of transmission. Using DOTS also prevents the development of drug-resistant strains of TB that are often fatal and very expensive to cure.[28] Multi-drug-resistant TB is both an individual tragedy and a reflection of poor program performance. The top priority is to prevent the emergence of MDR TB by ensuring a low default rate of cases treated with first-line anti-TB drugs. If MDR TB has emerged in a certain area, it should be treated in addition to improving the basic treatment. In this situation, accurate and reliable drug susceptibility testing, methods to support patients in order to ensure direct observation of complete treatment, and the use of maximally effective regimens must be ensured. Patients with MDR TB have a good chance for a cure with second-line drugs, hence the treatment, if it is to be provided, should be optimally selected and administered.[29] Second-line drugs should not be kept in reserve and the treatment observation must be ensured.

Cost and Cost effective analysis reviews

Kamolratanakul et al[33] (1993) From 1987-1989 They studied Cost-effectiveness analysis of three short-course anti-tuberculosis programmes compared with a standard regimen in Thailand. The study was undertaken to compare the efficacy, effectiveness and cost-effectiveness of three short-course regimens with a standard programme for treatment of new tuberculosis (TB) cases. The results showed that the three short-course regimens were more cost-effective than the standard regimen from the perspective of both providers and patients. Among the three short-course programmes, isoniazid, rifampicin and pyrazinamide for 2 months, followed by isoniazid and rifampicin twice a week for 4 months was the most cost-effective (US$70.24/effectiveness from providers' perspective and US$103.31/effective from patients' perspective). The result of this study throws some light on the development of new policy options, with scarce health resources, in the treatment of tuberculosis by the National Tuberculosis Programme in Thailand.

Floyd K et.al [34] In 1997 he studied cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. They compared 2 strategies1) the strategy used until the end of October 1997, which did not require any direct observation of treatment (DOT) and 2) a new community-based strategy introduced in November 1997, which required DOT by a community member 'guardian' or a health worker for the first 2 months of treatment. The finding showed that for new smear-positive patients, the cost per patient treated was dollars 456 with the conventional hospital-based strategy, and dollars 106 with the new decentralised strategy. Costs fell by 54% for health services and 58% for patients. The cost per patient cured was dollars 787 for the conventional hospital-based strategy, and dollars 296 for decentralised treatment. For smear-negative patients, the cost per patient treated was dollars 67 with the conventional unsupervised strategy, and dollars 101 with the community-based DOT strategy. Costs increased for health services, patients and guardians. Cost-effectiveness was similar with both strategies, at around dollars 200 per patient completing treatment.

Sterling [35] **et al.** (2003) studied Impact of DOTS compared with DOTS-plus on multidrug resistant tuberculosis and tuberculosis deaths: decision analysis.They used Monte Carlo simulation of a Markov decision tree by using people with smear positive pulmonary tuberculosis. And Analyses modelled different levels of program effectiveness of DOTS and DOTS-plus, and high (10%) and intermediate (3%) proportions of primary multidrug resistant tuberculosis, while accounting for exogenous reinfection. They found that the model predicted that under DOTS, 276 people would die from tuberculosis (24 multidrug resistant and 252 not multidrug resistant) over 10 years under optimal implementation in an area with 3% primary multidrug resistant tuberculosis. Optimal implementation of DOTS-plus would result in four (1.5%) fewer deaths. If implementation of DOTS-plus were to result in a decrease of just 5% in the effectiveness of DOTS, 16% more people would die with tuberculosis than under DOTS alone. In an area with 10% primary multidrug resistant tuberculosis, 10% fewer deaths would occur under optimal DOTS-plus than under optimal DOTS, but 16% more deaths would occur if implementation of DOTS-plus were to result in a 5% decrease in the effectiveness of DOTS

Mitnick [36] et al. (2002) from 1996-1999 studied Community-Based Therapy for Multidrug-Resistant Tuberculosis in Lima, Peru. They describe the first 75 patients to receive ambulatory treatment with individualized regimens for chronic multidrug-resistant tuberculosis in northern Lima. We conducted a retrospective review of the charts of all patients enrolled in the program between August 1, 1996, and February 1, 1999, and identified predictors of poor outcomes.They found that the infecting strains of Mycobacterium tuberculosis were resistant to a median of six drugs. Among the 66 patients who completed four or more months of therapy, 83 percent (55) were probably cured at the completion of treatment. Five of these 66 patients (8 percent) died while receiving therapy. Only one patient continued to have positive cultures after six months of treatment. All patients in whom treatment failed or who died had extensive bilateral pulmonary disease. In a multiple Cox proportional-hazards regression model, the predictors of the time to treatment failure or death were a low hematocrit (hazard ratio, 4.09; 95 percent confidence interval, 1.35 to 12.36) and a low body-mass index (hazard ratio, 3.23; 95 percent confidence interval, 0.90 to 11.53). Inclusion of pyrazinamide and ethambutol in the regimen (when susceptibility was confirmed) was associated with a favorable outcome (hazard ratio for treatment failure or death, 0.30; 95 percent confidence interval, 0.11 to 0.83).

Kamolratanakul [37] et al. (2002) from 1996-1997 studied cost analysis of different types of tuberculosis patient at tuberculosis centers in Thailand . They compared the total provider costs of delivering services to different types of TB patient in four zonal TB centers located in the east, northeast, north, and south of Thailand. This aim was accomplished by calculating the unit costs of TB treatment services at these TB centers during the year 1996-1997. All units of the zonal TB centers were classified into 5 cost-center categories: treatment units, laboratory units, radiology units, pharmaceutical units, and administrative/supportive units. The results showed that the average total provider cost of multi-drug resistant TB (MDR TB) patients was B 89,735.49 which was the highest of any type of patient and was 17 times higher than the cost of smear-negative TB cases; this finding was attributed to the high cost of anti-TB drugs for MDR TB cases (B 65,870), some 95 times higher than the cost for

smear-negative cases. Total provider costs were highest in the northeastern region TB centers and lowest in the southern centers for every type of TB patient: smear-negative TB cases (fl 7,727 vs fl 3,916), newly smear positive TB cases (fl 12,539 vs fl 7,020), TB with AIDS cases (fl 15,108 vs fl 8,369), re-treatment TB cases (fl 16,679 vs fl 9,696), and MDR TB cases (fl 102,330 vsfl 82,933). The information from this study may be useful when reviewing the role, function, and cost structure of each TB center in Thailand in order to establish a strategic plan for effective TB control.

Stephen C. Resch [38] et al. (2006) studied Cost-Effectiveness of Treating Multidrug-Resistant Tuberculosis. by developed a dynamic state-transition model of TB. In a base case analysis, the model was calibrated to approximate the TB epidemic in Peru, a setting with a smear-positive TB incidence of 120 per 100,000 and 4.5% MDR TB among prevalent cases. Secondary analyses considered other settings. The following strategies were evaluated: first-line drugs administered under directly observed therapy (DOTS), locally standardized second-line drugs for previously treated cases (STR1), locally standardized second-line drugs for previously treated cases with test-confirmed MDR TB (STR2), comprehensive drug susceptibility testing and individualized treatment for previously treated cases (ITR1), and comprehensive drug susceptibility testing and individualized treatment for all cases (ITR2). Outcomes were costs per TB death averted and costs per quality-adjusted life year (QALY) gained. We found that strategies incorporating the use of second-line drug regimens following first-line treatment failure were highly cost-effective compared to strategies using first-line drugs only. In our base case, standardized second-line treatment for confirmed MDR TB cases (STR2) had an incremental cost-effectiveness ratio of $720 per QALY ($8,700 per averted death) compared to DOTS. Individualized second-line drug treatment for MDR TB following first-line failure (ITR1) provided more benefit at an incremental cost of $990 per QALY ($12,000 per averted death) compared to STR2. A more aggressive version of the individualized treatment strategy (ITR2), in which both new and previously treated cases are tested for MDR TB, had an incremental cost-effectiveness ratio of $11,000 per QALY ($160,000 per averted death) compared to ITR1. The STR2 and ITR1 strategies remained cost-effective

under a wide range of alternative assumptions about treatment costs, effectiveness, MDR TB prevalence, and transmission. They concluded thatTreatment of MDR TB using second-line drugs is highly cost-effective in Peru.

Eliud Wandwalo[39] et.al. (2005) studied in 2002 for cost and cost-effectiveness of community based and health facility based directly observed treatment of tuberculosis in Dar es Salaam, Tanzania. They compared two alternative strategies : health facility based directly observed treatment by health personnel and community based directly observed treatment by treatment supervisors. Costs were analysed from the perspective of health services, patients and community in the year 2002 in US $ using standard methods. Treatment outcomes were obtained from a randomised-controlled trial which was conducted alongside the cost study. Smear positive, smear negative and extra-pulmonary TB patients were included. Cost-effectiveness was calculated as the cost per patient successfully treated. The results showed that the total cost of treating a patient with conventional health facility based DOT and community based DOT were $ 145 and $ 94 respectively. Community based DOT reduced cost by 35%. Cost fell by 27% for health services and 72% for patients. When smear positive and smear negative patients were considered separately, community DOT was associated with 45% and 19% reduction of the costs respectively. Patients used about $ 43 to follow their medication to health facility which is equivalent to their monthly income. Indirect costs were as important as direct costs, contributing to about 49% of the total patient's cost. The main reason for reduced cost was fewer number of visits to the TB clinic. Community based DOT was more cost-effective at $ 128 per patient successfully treated compared to $ 203 for a patient successfully treated with health facility based DOT.

Kominski, Gerald F.[40] et.al. (2007) in 2006 studied costs and cost-effectiveness of adolescent compliance with treatment for latent tuberculosis infection: results from a randomized trial.they assigned adolescents between the ages of 11 and 19 years who were referred to one of two participating clinics after being screened for TB and receiving a positive diagnosis indicating LTBI (n = 794) to one of four groups: usual care, peer counseling, contingency contracting, and combined peer

counseling/contingency contracting. Primary outcome variables were completion of isoniazid preventive therapy (IPT), total treatment costs, and lifetime TB-related costs per quality-adjusted life year (QALY) in each of the four study groups (three treatment, one control). Cost effectiveness was evaluated using a five-stage Markov model and a Monte Carlo simulation with 10,000 trials. The results showed that average costs were 199 dollars for usual care (UC), 277 dollars for peer counseling (PC), 326 dollars for contingency contracting (CC), and 341 dollars for PC+ CC combined. The differences among these groups were all significant at the p = .001 level. Only the PC + CC group improved the rate of IPT completion (83.8%) relative to usual care (75.9%) (p = .051), with an overall incremental CE ratio of 209 dollars per QALY relative to usual care. They concluded that : Incentives combined with peer counseling are a cost-effective strategy for helping adolescents to complete care when combined with peer counseling.

Lydia Kivihya-Ndugga [41] et.al (2003) studied the comparison of PCR with the Routine Procedure for Diagnosis of Tuberculosis in a Population with High Prevalences of Tuberculosis and Human Immunodeficiency Virus. Sputum specimens were collected from 1,396 TB suspects attending the Rhodes Chest Clinic, Nairobi, Kenya. The specimens were analyzed for the presence of Mycobacterium tuberculosis by PCR; culture on L**Ö**wenstein-Jensen medium was used as the "gold standard." All culture-positive samples were genotyped to identify the mycobacterial species. The sensitivity and specificity of PCR were 93 and 84%, respectively. HIV status did not affect the sensitivity of PCR. A total of 99.7% of the true smear-positive and 82.1% of the true smear-negative TB patients were correctly identified by PCR. PCR detected M. tuberculosis in 11.7% of the culture-negative suspects, 60% of which had one or two PCR-positive sputum specimens. Of the 490 positive cultures, 486 were identified as M. tuberculosis. The high sensitivity of Amplicor PCR merits usage in a clinical setting with high TB and HIV burdens. Thus, PCR can be considered as an alternative to ZN staining in combination with chest X-ray for diagnosis of TB; however, cost-effectiveness studies and operational studies are

required to support an evidence-based decision of introducing PCR for TB control in high-burden environments.

Kangovi S et.al.[42](2009) reviewed a classification and meta-analysis of community-based directly observed therapy programs for tuberculosis treatment in developing countries. And found that Ten major features define CBDOT program structure and function. Programs that paid their CBDOT providers tended to differ from unpaid programs based on all of these features. CBDOT programs in which providers received financial reward had success rates of 85.7 versus 77.6% in programs without financial reward for providers. This difference was not statistically significant. CBDOT programs fall into two major archetypes, which differ in their structure and possibly in their outcomes.

Kabongo et.al.[43](2010) had studied the effectiveness of home-based directly observed treatment for tuberculosis in Kweneng West subdistrict, Botswana. with a quantitative, observational study using routinely collected TB data from 405 TB patients and combined with 20 qualitative in-depth interviews. They found that the overall cure rate for smear-positive pulmonary TB patients was 78.5%. Treatment outcomes were not statistically different between FB-DOT and HB-DOT. Contact tracing was significantly better in FB-DOT patients. Interviews revealed advantages and disadvantages for both FB and HB options and that flexibility in the choice or mix of options was important. A number of suggestions were made by the interviewees to improve the HB-DOT programme. And had concluded that HB-DOT is at least as good as FB-DOT in terms of the treatment outcomes, but attention must be given to contact tracing. HB-DOT offers some patients the flexibility they need to adhere to TB treatment and community volunteers may be strengthened by ongoing training and support from health workers, financial incentives and provision of basic equipment.

Floyd K et.al.[44](2003) had study the Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. By introduced to assess the cost and cost-effectiveness of new treatment strategies for new pulmonary tuberculosis patients, in 1997. And compared two strategies for new smear-positive pulmonary patients 1) the strategy used until

the end of October 1997, involving 2 months of hospitalisation at the beginning of treatment, and 2) a new decentralised strategy introduced in November 1997, in which patients were given the choice of in- or outpatient care during the first 2 months of treatment. For new smear-negative pulmonary patients, the two strategies compared were 1) the strategy used until the end of October 1997, which did not require any direct observation of treatment (DOT) and 2) a new community-based strategy introduced in November 1997, which required DOT by a community member 'guardian' or a health worker for the first 2 months of treatment. Costs were analysed from the perspective of health services, patients, and the community in 1998 US dollars, using standard methods. Cost-effectiveness was calculated as the cost per patient cured (smear-positive cases) and as the cost per patient completing treatment (new smear-negative cases).There findings for new smear-positive patients were the cost per patient treated was dollars 456 with the conventional hospital-based strategy, and dollars 106 with the new decentralised strategy. Costs fell by 54% for health services and 58% for patients. The cost per patient cured was dollars 787 for the conventional hospital-based strategy, and dollars 296 for decentralised treatment. For smear-negative patients, the cost per patient treated was dollars 67 with the conventional unsupervised strategy, and dollars 101 with the community-based DOT strategy. Costs increased for health services, patients and guardians. Cost-effectiveness was similar with both strategies, at around dollars 200 per patient completing treatment. When new smear-positive and new smear-negative patients were considered together, the new strategies were associated with a 50% reduction in total annual costs.And concluded that There is a strong economic case for expansion of decentralisation and community-based DOT in Malawi. Further investment in training and program supervision may help to increase effectiveness. Doungnate Tonimit [45] (2000) had investigated cost-effectiveness between DOTS and SAT by using a retrospective cohort design conducted on a cohort of 204 new pulmonary TB patients with sputum smear positive, regardless of HIV status. All registered patients between October 1, 1998 and March 31, 1999 were followed up until the occurrence of events or the day of study termination (November 30, 1999)

and a cost per case cure was calculated for each strategy. In general, the TB patients were mostly unskilled male workers with the mean age of 45 years, graduated from primary school level. There was a high death rate particularly among smoking males aged 15-34 years. Results revealed that the proportion of defaulters at the second month of treatment was 2.6% for DOTS compared with 11.5% for SAT. The median time-to-cure among the DOTS group (184 days) was shorter than those among the SAT group (210 days). Their findings evidence that the cure rate of patients under DOTS (67.5%) was significantly higher than that under SAT (34.5%) with the net gain of 96%. The unadjusted analysis showed that patients under DOTS were more likely to be cured at 1.96 times higher than that of SAT ($p<0.01$). Using Cox's proportional hazard model, the patients treated under DOTS had the estimated relative hazard at 2.91 (95% CI 1.70-4.70) compared with those under SAT after adjusting for occupation and residence. Although an average cost per patient treated under DOTS (7,363 Baht) was higher than those under SAT (5,422 Baht), the difference was not statistically significant ($p=0.77$). In fact, a cost per case cured under DOTS (10,905 Baht) was lower than those under SAT (15,724 Baht). Sensitivity analysis indicated that the advantage of cost-effectiveness of DOTS and SAT was sensitive to cure rate but not for travel cost and labour cost. Moreover, sensitivity results indicated that the net gain between the two programs should be at least 36% in order to maintain an economic advantage of DOTS over SAT. And concluded that, DOTS offer a higher cure rate than SAT resulting in increased cost savings for public health, thus DOTS is superior to SAT for TB control programs. Further investigation on high death rates and implementing a modified DOTS (M-DOTS) strategy in SAT setting are recommended.

David and Daniel[46] (1999) had determined the incremental cost of directly observed therapy (DOT) for patients with tuberculosis at low risk for treatment default, by applied a model of DOT effectiveness to 1,377 low-risk patients in California during 1995. The default rate for their cohort, which consisted of those with no recent history of substance abuse, homelessness, or incarceration, was 1.7%. The model predicted that DOT and self-administered therapy (SAT) cured 93.1 and 90.8% of these patients, respectively. DOT would initially cost $1.83 million more than SAT, but avert

$569,191 in treatment cost for relapse cases and their contacts, for a net incremental cost of $1.27 million ($919 per patient treated), or $40,620 per additional case cured. The cost-effectiveness of DOT was sensitive to the default rate and relapse rate after completing SAT. DOT would generate cost savings only when the default and relapse rates were more than 32.2 %and 9.2%, respectively. Given the low default rate and resulting high incremental cost of DOT, provision of DOT to low-risk patients in California should be evaluated in the context of resource availability, competing program priorities, and program success in completing self-administered therapy with a low relapse rate.

Carlos Acuna-Villaorduna [47] et.al (2003) had study Cost-Effectiveness Analysis of 5 DST methods in the context of a clinical trial that compared rapid with conventional DST methods. The methods under investigation were direct phage-replication assay (FASTPlaque-Response; Biotech), direct amplification and reverse hybridization of the *rpoB* gene (INNO-LiPA; Innogenetics), indirect colorimetric minimum inhibitory concentration assay (MTT; ICN Biomedicals), and direct proportion method on L**Ö**wenstein-Jensen medium. These were compared with the widely used indirect proportion method on L**Ö**wenstein-Jensen medium. They found that all alternative DST methods were found to be cost-effective, compared with other health care interventions. DST methods also generate substantial cost savings in settings of high prevalence of multidrug-resistant tuberculosis. Excluding the effects of transmission, the direct proportion method on L**Ö**wenstein-Jensen medium was the most cost-effective alternative DST method for patient groups with prevalences of multidrug-resistant tuberculosis of 2%, 5%, 20%, and 50% (cost in US$2004, $94, $36, $8, and $2 per disability-adjusted life year, respectively).

Okello D et.al.[48](2003) had studied in rural Uganda about the cost and cost-effectiveness of community-based care for new smear-positive pulmonary tuberculosis patients compared with conventional hospital-based care by analysis the costs from the perspective of health services, patients, and community volunteers in 1998 US dollars, using standard methods. Cost-effectiveness was calculated as the cost per patient successfully treated. And they found that the cost per patient treated

for new smear-positive patients was dollars 510 with the conventional hospital-based approach to care (dollars 419 for the health system and dollars 91 for patients), and dollars 289 with community-based care (dollars 227 for health services, dollars 53 for patients and dollars 9 for volunteers). Important new costs associated with community-based care included programme supervision (dollars 18 and dollars 9 per patient at central and district levels, respectively) and training (dollars 18 per patient). The cost per patient successfully treated was dollars 911 with the hospital-based strategy and dollars 391 with community-based care, reflecting both lower costs and higher effectiveness (74% vs. 56% successful treatment rate) with community-based care. Length of hospital stay fell from an average of 60 to 19 days.

CHAPTER 3

Research Methodology

Research design

An open label, multi centers, Randomize control trial study.

Research Methodology

Study location

For patients treatment and follow up: all government hospitals in upper northern 7 provinces (Chaing Mai, Lumpoon, Phayao, Lumpang, Chiang Rai, Prae, and Nan). Main hospital will be 8 general/regional hospitals

For laboratory procedure including identification of microbes and drugs sensitivity test: the central laboratory and Tuberculosis section of Office of Disease Prevention and Control region 10.

For data collection and data analysis: Office of Disease Prevention and Control region 10

Population

Target population

New cases of (sputum smear positive pulmonary tuberculosis patients) both non MDR-TB and MDR-TB who are diagnosed in the upper north of Thailand

Study population

New cases of sputum smear positive pulmonary Tuberculosis patients both non MDR-TB and MDR-TB who are diagnosed in the government hospitals in 7 provincial hospital in the upper northern region of Thailand between May 2009 – December 2009

Once diagnosed with pulmonary TB by the doctor, the sputum will be sent to TB center region 10

* to test whether the patient is infected with M. Tuberculosis or not using PCR

technique (extract by Boom technique, amplification by NASBA technique, and detection by Molecular technique)[30-32]

* to do DST using proportion method of The National Committee for Clinical Laboratory Standards (NCCLS)

* Both laboratory results will be reported back to the hospital within one month

Eligibility criteria

Inclusion criteria:

1. Identify by PCR to be *M. Tuberculosis* after had smear positive
2. Never been treated with 2nd line drug anti-TB chemotherapy
3. Age 15 years old or older

Exclusion criteria

1. Pregnancy / lactation and had history of epilepsy and Alcoholism
2. Unable to communicate with the investigators / health care personnel
3. The bacteria is resisted to Isoniazid, Rifampicin together with Kanamycin+ +Ofloxacin+ Pyrazinamide+ PAS (XDR)

Discontinuation Criteria for participant

1. Lost to follow up
2. Death and transfer out

Sample size

The formula used to calculate the optimum sample size[49]

$$N = \frac{\{ Z\alpha\sqrt{2pq} + Z\beta\sqrt{P1[1+R-P1^{(1+R2)}]} \}^2}{\{ P1^{(1-R)} \}^2}$$

Projected RR = 2, α = 0.05 = 1.96, β = 0.05 = 1.64

Expected cure rate for MDR-TB group from previous study = 65%[12]

(P1 = 0.65), n = 18.68

Expected cure rate for non MDR-TB group from previous study = 70%[2]

(P1 = 0.70), n = 29.80

When cure rate was lower than 85% RR for MDR-TB would be higher than 1

We will add 10% of sample size to return subject who will leave from the study so the sample size should be as follow :-

- Sample size for MDR-TB = 19 cases / arm
- Sample size for non MDR-TB = 30 cases / arm

Study samples, sampling strategy, and enrollment

The patients with sputum smear positive TB and drug resistant TB and qualification as Inclusion criteria from the hospital sending sputum specimen to be tested were explained on tuberculosis and aids by nurse or officer in charge of the hospital, together with details in the project introduction document. After such information was given and the patients had time to make decision to join the project, they were inquired on their wish towards the project. The patient willing to join the project received a letter of consent to be signed and then the attendance and treatment were provided to them according to procedure of the project.

Selection of patients for the intervention group and control group

1) When the patients had passed AFB test and DST test, in case of the patient with drug resistant TB found, the ones with non-pulmonary tuberculosis(NTM) were screened out, remaining the ones with Mycobacterium Tuberculosis (MTB) to be selected to join the comparative experimental study project conducted with randomization.

2) In case that the selected patients are the intervention group, the officer in charge notified the patient and coordinated on disbursement of drug from VMI system for the patients to take at home, together with explaining how to get injection of and take drug, where every meal the patients were followed up taking the drug as prescription by mobile phone provided by the project for the patients who did not have telephone. And the patients were appointed to receive the drug on monthly basis.

3) In case that the selected patients are the control group,the officer in charge notified the patient and coordinated on disbursement of drug from VMI system for the patients to take at home, together with explaining how to get injection of and take drug and following up drug injecting and taking of the patients according to the prescription as same as the study group but they were followed up by AIDS/TB volunteers every month for 18 months without using mobile phone.

4) The pharmacist of the hospital was charged to prepare disbursement of drug from VMI system of the host hospital for the patients and provide drug counseling.

5) Every month, the patients had to be appointed for physical examination, sputum specimen test. The officer in charge notified the patients to bring their sputum

specimen to be tested for following the result of treatment, total 2 specimens, and see if the patients were completely cured in those two groups of subjects.

6) All patients joining the project were registered as the patient with TB according to normal system of NTP. The result of response to anti-TB drug of those two samples was recorded in the form designed specifically for data collection according to the form in the appendix which DTC of general hospital will be collected.

Allocation of treatment

Each subject will assigned to treatment or control group with systemic randomized from laboratory of TB central ,The Office of DISEASE Prevention and Control,10

Figure 2 : Diagram for intervention in MDR-TB group

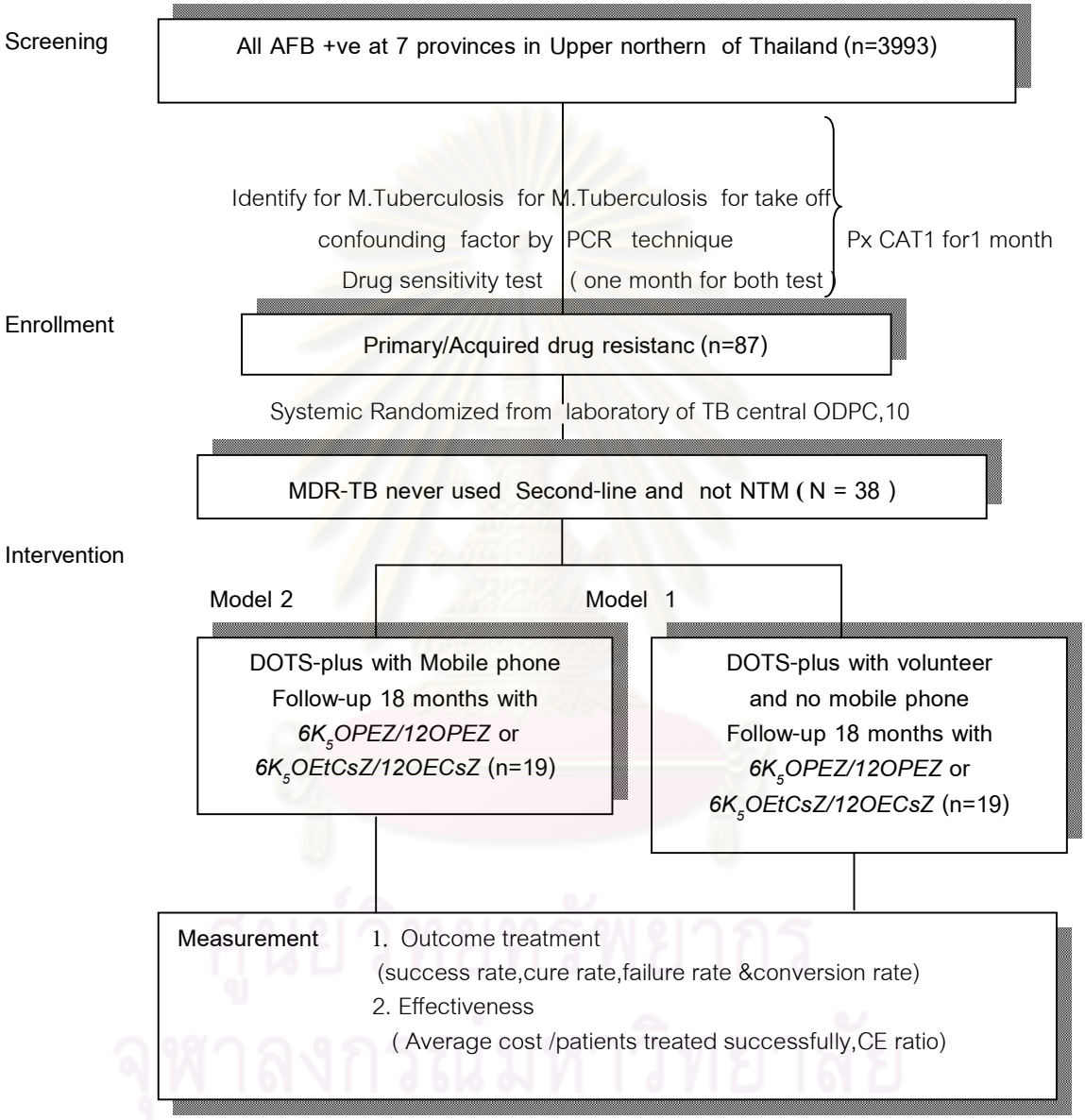
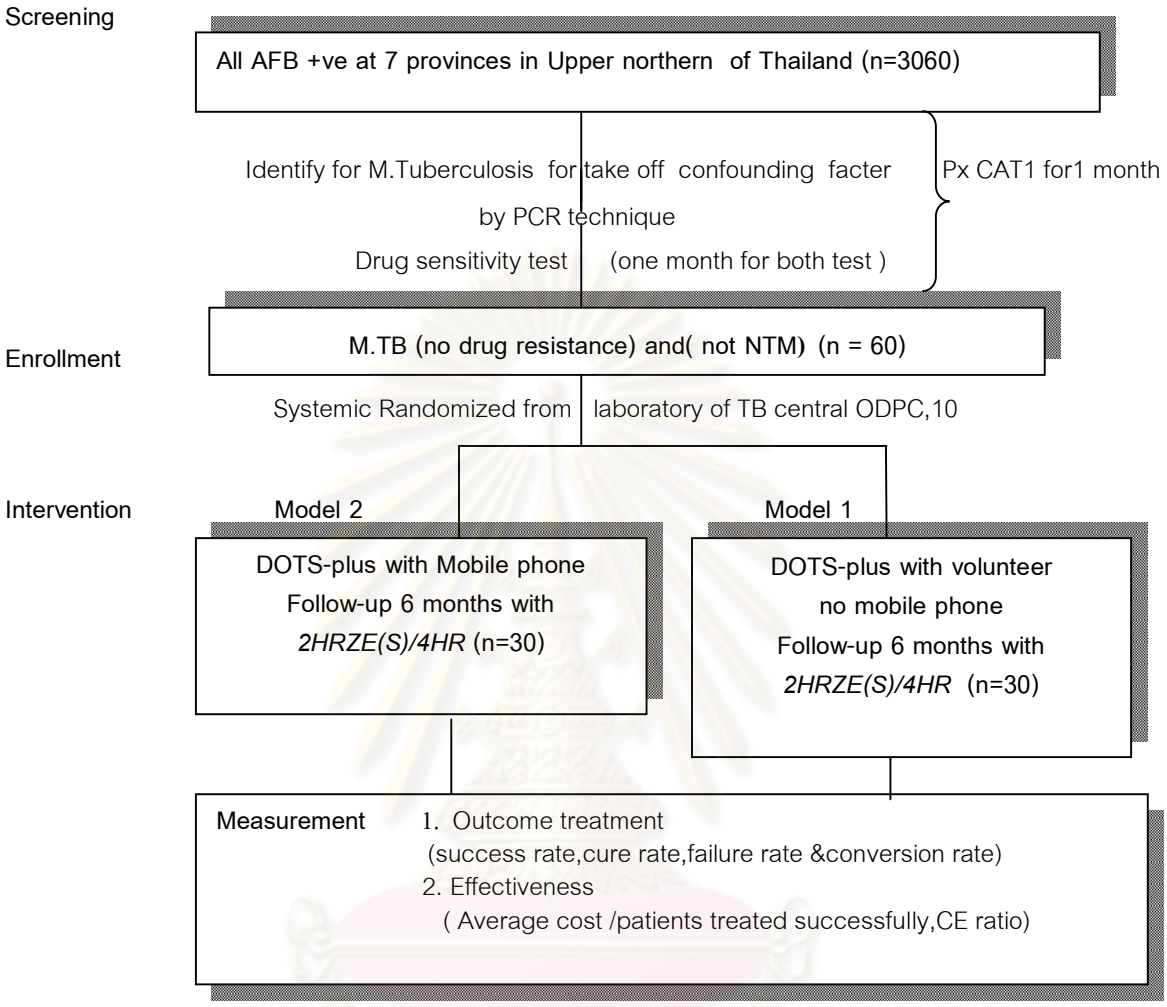


Figure 3 : Diagram for intervention in non MDR-TB group



Materials and Methods

For this study, the model of TB control is defined into 2 models as follow:

Model 1 was the model that process on DOTS-Plus with non mobile phone or with volunteer)

Step 1: Screen NTM patient out of TB patient with AFB positive sputum specimen

Step 2: Perform Drug Sensitivity Test (DST)

Step 3: Provide care according to the way of WHO [12] for MDR-TB treatment using normal DOT

Model 2 was the model that process on DOTS-Plus with mobile phone

There are 3 steps same as model 1. The different point is on step 3 including the service of communication to remind the patient for medication via mobile phone additionally.

Operating Procedure:

The meeting was held to explain steps of operation and filling of forms of the project to networks attending the project as follow:

Step 1: To screen NTM patients using molecular technique [30-32]. This was conducted at TB Center Zone 10, Chiang Mai, when the AFB positive sputum specimen was received from the hospital in the area of study.

Step 2: To test TB drug sensitivity applying Proportional Method of National Committee for Clinical Laboratory Standards (NCCLS), containing both First line drugs and Second Line Drugs, that is, *Isoniazid (H), Rifampicin (R), Streptomycin (S), Ethambutol (E), Kanamycin (K),* and *Ofloxacin (O)*

Step 3: The hospital in the area of study gave information to the patient in case that the patient has MDR-TB and was randomized to attend the project. When the patient signed for giving consent to attend the project, such patient would be enrolled as a project patient and they would be treated according to WHO guide for MDR-TB applying normal DOT method for the group of model 1, and DOT with using mobile phone for the group of model 2. And the physicians in charge of TB clinic of the hospital in the area of study were given counsel by specialist via telephone at anytime they found the problem.

The intervention

For control group with MDR-TB

Group of Model 1: This is a group of patients who were found MDR-TB from the result of DST and given consent to attend the project. These patients were treated with medicine in formula according to WHO guide-line, that is, *$6K_5OPEZ/12OPEZ$* in case that they resist HR, HRS. And if any patients resist HRE or HRSE, they will be given medicine in formula of *$6K_5OPEtZ/12OPEtZ$* for treatment. These patients had to come to receive the medicine at the central hospital or general hospital in the area they live or TB Center Zone 10, Chiang Mai. And they were visited by TB volunteer every month until the end of treatment course of 18 months.

For experiment group with MDR-TB

Group of Model 2: This is a group that were provided treatment same as the group of model 1 in all respects but they were given counsel and reminded for medication via mobile phone for every meal they had to take the medicine by officer of TB Center Zone 10, Chiang Mai. In case that any patient had no mobile phone, such patient would be given a mobile phone with SIM Card enabling them to receive the call of reminding them for medication or giving counsel in case of problem from taking medicine, and making appointment to come to receive the medicine and be examined on sputum specimen every month, with explanation to make them clear that they were asked to keep the mobile phone on in order to be remind for medication every meal by the officer.

For control group with non MDR-TB

Group of Model 1: This is a group of patients who were found non MDR-TB from the result of DST and given consent to attend the project. These patients were treated with medicine in formula according to the national TB control program , that is, *2HRZE(S)/4HR* for treatment. These patients had to come to receive the medicine at the community hospital in the area they live to have physical check up by nurse, sputum examination,

And they were visited by TB volunteer every month until the end of treatment course of 6 months. (from the day of AFB positive)

For experiment group with non MDR-TB

Group of Model 2: This is a group that were provided treatment same as the group of model 1 in all respects but they were given counsel and reminded for medication via mobile phone for every meal they had to take the medicine by officer of TB Center Zone 10, Chiang Mai. In case that any patient had no mobile phone, such patient would be given a mobile phone with SIM Card enabling them to receive the call of reminding them for medication or giving counsel in case of problem from taking medicine, and making appointment to come to receive the medicine and be examined on sputum specimen every month, with explanation to

make them clear that they were asked to keep the mobile phone on in order to be remind for medication every meal by the officer

Research instruments

This study was a systemic randomized control trial study design . The research instruments were :-

1. Drug adherence book record and mobile phone communication record
2. Laboratory exam (sputum for AFB , culture, Drug susceptibility testing,
3. Identity for TB testing , and blood chemistry)
4. Physical exam result and Chest X-ray result

Outcome measurement

- We measured of - treatment outcome
- average cost per patient treated successfully and CE-ratio

Data collection and management for effectiveness

1. Each subject will be registered into TB clinic of particular hospital
2. Each subject will be assigned a unique patient identification number
3. Clinical data will be confidential as used only by health staff and investigators
4. All specimens sent to the laboratories will have no patient name attached an use only patient identification numbers
5. All data will be input into data files and kept secret. Only investigators will have access to the files.

Data collection and management for effectiveness

We collected data by the form and the responsibility of data record and frequency as in table 7

Table 7 Data Collection

Data Collection	Time record	Responsibility	Record Form
1. TB factor	After enrollment	Nurse of Regional/general hosp for MDR-TB and Nurse of community hosp for Non MDR-TB	Form 1-3,10
2. Drug adherence	Every month	"	Form 4.1-4.7
3. Labboratory exam			Form 5-6,8-9
3.1 AFB/culture	Every month	"	Form 06.1
3.2 DST	Before enrollment	"	Form 06.1
3.3 Identify for MTB	Before enrollment	"	Form 06.1
3.4 LFT/bl chemistry	Every 3 mont	"	Form 06.2
4. Chest X-ray	Every 6 month	"	Form 4.1
5. Physical exam	Every month	Doctor of Regional/ general hosp for MDR-TB and Nurse of community hosp for Non MDR-TB	OPD card for TB patient
6. Mobile phone communication	Everyday	TB center 10.	Form 07 with content- Drug taken,TbB drug side effect and General health of patient

Procedure 1-6 do by medical staff at Regional hospital/General hospital in home province of patient&do to both group . Researcher will monitor data-record every 2 month.

Data analysis

Data of monitoring on MDR-TB was collected from access database from TB system of Thailand MOPH –U.S. CDC Collaboration (TUC). Summary statistic for continuous variable were present as mean and standard deviation(SD). Univariate analysis was performed using Fisher's exact test for categorical and Wilcoxon's test for continuous variable.

The endpoint were cure rate,complete rate, failure rate and success rate, for 18 months for MDR-TB group and 6 months for non MDR-TB group and also conversion rate at 1 month for both group.

Conversion was estimated using the Kaplan-Meire method. The difference in conversion rates was determined using the log-Rank test.

All outcome were compared between DOTS-Plus with mobile phone group(model 1) and DOTS-Plus without mobile phone group (model 2). Kaplan-Meire estimates were used to compare the differences of conversion event of both groups(MDR-TB & non MDR-TB).

All P values were two-sided,and P values <0.05 were considered to be statistically significant. Statistical analyses were performed by using STATA(version 10.1) and Epi Info programe (version 6).

Cost Analysis

Costs were assessed from societal perspective and was performed according to provider and patient perspective.

The provider cost data was collected from health care delivery system, tuberculosis control program at regional, provincial,and community level. The direct medical care costs could be devided into 2 component.

1. labor costs: These were the payments for 1) time compensation for doctors, nurse,and pharmacists. 2) telephone call. 3) laboratory task,and 4) volunteer costs for DOT visit.

2. non labor costs were for medications,labolatory materials,culture medium for AFB,C&S,DST, and microbes identification. These category of expenses also covered cost of blood chemistry tests,chest X-ray,logistics,telephone bills,management, and monitoring. All the unit costs were calculated as charge costs and not included capital costs.

The source of provider cost came from health care system as below :-

Category of cost	Source of cost
1. Drugs	1. Price list of drug (TB center,ODPC10 ,2010)
2. Laboratory Material for AFB,C&S,DST,Identify	2. Price list of material (TB center,ODPC10,2010)
3.Blood chemistry(BUN,Cr,SGOT,SGPT)	3. Comptroller General's Department
4.Chest X-ray	4. Comptroller Generall's Department
5. Mobile phone package	5. CAD telecom(2009) AIS (2010)
6.Personal payment for mobile phone call	6.Regional program of ODPC10(2010)
7.Program management and staff costs	7. Regional&provincial program in region 15,16 (2010)

Patients costs was collected using a structured interview questionnaire. The transportation cost was considered as direct cost in this case. Indirect costs included patients'income lost from work absence due to visiting the TB clinic. The daily lost was calculated from each patient's monthly income. The income lost of the relatives who accompanied the patients to TB clinic also considered as indirect cost and was calculated in the same way.

Outcome

Effectiveness : The effectiveness was measured as the average increasing of the success rate of treatment outcome. Data on treatment outcomes were obtained from the randomized-controlled trial and operational definitions used in this study are explained in detail below.

Non MDR TB group

Out come assessment was undertaken by labolatory examination of sputum by technicians unaware of treatment allocation. Standard International Union Against Tuberculosis and Lung Disease/WHO outcomes were used to measure effect.

A patient was classified as cured if comfirmed to be sputum negative at 6 months and at least one previous occasion .

A patient was classified as having completed treatment if treatment was completed but smear results were not available on at least two occasions prior to completion of treatment.

Treatment failure was recored for patients who remained or became positive at 5 months or later.

MDR TB group

Treatment success for MDR TB group included patients who were cured and those who completed treatment (Cure + Complete treatment). Cured patients will be those with positive sputum smear before starting treatment and confirmed to be sputum negative at 7(or 8) months and at least one previous occasion. Treatment success is used in routine practice to refer to smear positive patients who are cured and have completed treatment

Completed treatment for MDR TB group applied to: patients who had positive pre-treatment results, negative results at 2 months, and no end of treatment results; patients who had negative pre-treatment results and had been placed on treatment for clinical reasons, and patients who completed the full course of treatment, but had no pre-treatment or end-of-treatment bacteriological results.

Calculate of treatment outcome

When A = Number of evaluate case

a = Number of cure patients

b = Number of complete treatment patients

c = Number of failure patients

d = Number of died patients

e = Number of default patients

f = Number of transfer out patients

Cure rate = (a/A) x 100

Complete rate = (b/A) x 100

Failure rate = (c/A) x 100

Death rate = (d/A) x 100

Default rate = f/A) x 100

Treatment success = Cure + Complete treatment

Cost effectiveness will be calculated as the average cost per patient treated successfully. This will be done by dividing the total cost and patients successfully treated. (CE ratio).

CE ratio = $\frac{\text{Cost DOTS-Plus with mobile phone- Cost DOTS-Plus without mobile phone}}{\text{effect DOTS-Plus with mobile phone- effect DOTS-Plus without mobile phone}}$

CHAPTER 4

Result and Analysis

From screening the patients having TB positive sputum specimen by using microscope from April 2008 to September 2009, total 3993 persons, NTM is found for 264 persons or 6.6 percents according to table 8.

Table 8 Number and percentage of TB screening for NTM infection in Upper Northern Thailand during Apr 08-Sept 09

Result of exam	NUMBER n =3993	Percentage
No growth	495	12.3
Contaminate	174	4.4
NTM infected	264	6.6
Non NTM	3060	76.6

And from all sorted NTM out, when TB drug sensitivity testing was performed, MDR-TB was found for 87 persons or 2.8 percents as detailed in table 9.

Table 9 Number and percentage of TB screening for MDR- TB in Upper Northern Thailand during April 2008-September 2009

Province	Number		Percentage
	Exam	MDR-TB	
Total of 7 provinces	3060	87	2.8

From total of 87 MDR-TB patients, 38 patients could be enrolled into the project,and from 2980 non MDR-TB patients 60 patients could be enroll into the project separated into group of study and characteristics of population as table 10.1-10.2

Table 10.1 Baseline demographic and clinical characterisrics of MDR-TB groups

Demographic&Clinical Characteristics		Mobile phone group n=19	Non Mobile phone group n=19	p-value
Sex	Male	12(63.2%)	12(63.2%)	1.00
	Female	7(36.8%)	7(36.8%)	
Mean Age yr (sd)		35.8(±12.4)	45(±15.6)	0.496
Type of patient	New	7(36.8%)	6 (31.6%)	0.732
	Relaps/TAD	12(63.2%)	13 (68.4%)	
HIV infection	Infected	2(10%)	1(5%)	1.00
	Not Infected	17(90%)	18(95%)	
ill with DM	DM	5(25%)	2(10%)	0.405
	no DM	14(75%)	17(90%)	

Table 10.2 Baseline demographic&clinical characterisrics of Non MDR-TB groups

Demographic&Clinical Characteristics		Mobile phone group n=30	Non Mobile phone group n=30	p-value
1. Sex	Male	20(66.7%)	19(63.3%)	0.661
	Female	10(33.3%)	11(36.7%)	
2. Mean Age yr (sd)		50.1(±19.0)	56.0(±14.5)	0.094
3. Marital status	Single	4(13.3%)	3(10.0%)	0.511
	Couple	19(63.3%)	23(76.7%)	
	Widow	7(23.3%)	4(13.3%)	
4. Education	No literacy	6(26.1%)	7(23.3%)	0.870
Primary/Secondaly school		21(70.0%)	21(70.0%)	
High school/university		3(10.0%)	2(6.7%)	
5. Type of patient	New	28(93.4%)	30(100%)	0.350
	Relaps/TAD	2(6.6%)	0	
6. TB Drug resistance	yes	1(3.3%)	0	0.500
	no	29(96.7%)	30(100%)	
7.HIV infection	Infected	2(6.7%)	4(13.3%)	0.389
	Not Infected	28(93.3%)	26(86.7%)	
8. ill with DM	DM	5(16.7%)	6(20%)	0.738
	no DM	25(83.3%)	24(80%)	

X^2 test for p-value

By the way, mostly characterisrics of sample are not different but it was found that in MDR-TB group the group of model 2 had ratio of diabetes higher than the group of model 1.

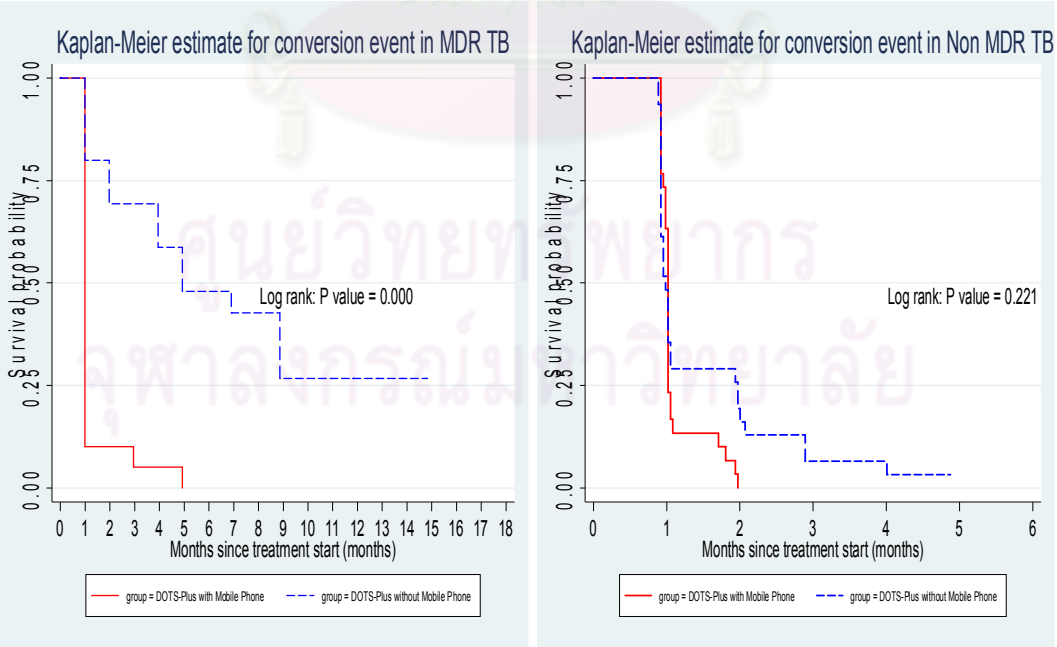
When treatment outcome of the patients enrolled into the project of those 2 group were followed up, it is found that the patients of group of model 2 had rate of change positive result of sputum test to be negative within 1 month higher than the group of model 1 .

In the MDR-TB group, Figure 4(a), probability of sputum not conversion within 1 month was 10%(95%CI 2%-27%) in DOTS-Plus with mibile phone and was 80%(95%CI,55%-92%) in DOTS-Plus without mobile phone .

In the non MDR-TB group, Figure4(b), probability of sputum not conversion within 1 month was 63%(95%CI,44%-78%) in DOTS-Plus with mobile phone and was 48%(95%CI,30%-64%) in DOTS-Plus without mobile phone.

However,there were statistically significant in non MDR-TB group (p-value<0.001) but were not statistically significant in non MDR-TB group (p-value=0.221) between two groups of patients.

Figure 4 Kaplan-Meire estimate for sputum conversion event by model implementation in MDR-TB group during 18 months of treatment (a) and in non MDR-TB group during 6 months of treatment (b)



(a) (b)

When treatment outcome of MDR and non MDR TB groups had treated full 6 months, and 18 months it is found that the samples of group of model 2 in both MDR and non MDR-TB group had success rate in high level as 100 percents while the group of model 1 had success rate only 73.7% with in MDR group and 96.7% in non MDR group. Both MDR and non MDR TB groups there was no failure rate found in the group of model 2 while failure rate of the group of model 1 is 26.3% and 3.3% respectively. They are different significantly in statistic at p=0.0001 for MDR group and p=0.047 for non MDR TB group as the result in table 11.

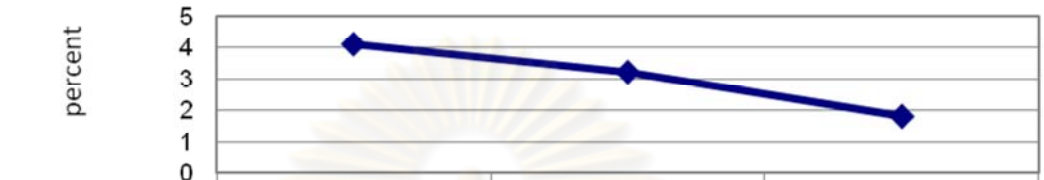
Table 11 Treatment Outcome of MDR and non MDR TB groups by model implementation

Treatment Outcome	MDR-TB group(n=38)		Non MDR-TB group(n=61)	
	Model 1 non mobile phone gr n=19	Model 2 mobile phone gr n= 19	Model 1 non mobile phone gr n=30	Model 2 mobile phone gr n=30
1. Cure rate	6(31.6%)	19(100%)	23(76.7%)	30(100%)
2. Complete rate	8(42.1%)	0(0%)	6(20.0%)	0(0%)
3. Failure rate	5(26.3%)	0(0%)	1(3.3%)	0(0%)
4. Success rate	14(73.7%)	19(100%)	29(96.7%)	30(100%)
p-value	0.0001		0.047	

X^2 test for p-value

And when trend of MDR-TB in northern area of Thailand was monitored from April 2008 to September 2009, it shows that the prevalence trend of MDR-TB is decreased as detailed in figure 5

Figure 5 Trend of MDR-TB rate in Upper north, Thailand during april 2008-september 2009



For the result of cost analysis : We found that the total cost between Mobile phone and non mobile in MDR-TB and non MDR-TB group were not different as in table 11.1,11.2 .

The total cost of MDR-TB with Mobile phone group was baht 2,422,605 and without mobile phone was baht 2,430,085 as in table 11.1

The total cost of non MDR-TB with Mobile phone group was baht 446,720 and without mobile phone was baht 447,320 as in table 11.2

The total cost of MDR and non MDR-TB with Mobile phone group lower than the group that unused mobile phone only baht 7,480 in MDR-TB and baht 600 in non MDR-TB group

The average total cost per patient of MDR and non MDR-TB with Mobile phone group was baht 127,506 and 14,890.67 as in table 12

The average total cost per patient of MDR and non MDR-TB without Mobile phone group was baht 127,899 and 14910.67 as in table 12

The average total cost for cure was not different significant in both group respectively (p-value= 0.674) as in table 12

* In table 11.1,11.2 The high cost of non mobile group was from volunteer cost and the cost of laboratory labor in case of sputum still positive. Sputum should have to culture and test for drug sensitivity.and should have more cost for specimen transportation.

Table 11.1 The total cost of managing a TB patient to treatment completion between mobile phone& Non mobile intervention in MDR group

Cost Analysis Direct cost A. Provider cost	Unit cost per patient	MDR-TB gr(n=38)	
		Mobile(N=19)	Non Mobile(N=19)
		Total cost	Total cost
A1 Drug regimen * 6K5OPEZ / 12OPEZ	38,970	272,790	272,790
* 6K5OEtCsZ / 12OErCsZ	114,600	1,375,200	1,375,200
A2 Material for Sputum Smears 18 times	1,080	20,520	20,520
A3 Material for Sputum Cultures 18 times	3,600	68,400	68,400
A4 Material for Sputum DST 1 time	100	2,400	2,400
A5 Material for Sputum for Identity NTM 1 time	350	6,650	6,650
A6 Specimen transportation 18 times	240	13,680	13,680
A7 Lab labor * AFB+C/S+ PCR+DST	556.6/mobile	10,575	14,470
	761.6/non mobile		
A8 BUN , Creatinine, SGOT, SGPT	1,320	25,080	25,080
A9 X-rays	240	4,560	4,560
A10 Overall follow-up/Supervision	2,295	43,605	43,605
A11 Program management at regional/provincial level for conference meeting	15,610	296,590	296,560
A11.1 doctor charge per month	900	17,100	17,100
A11.2 pharmacist charge per month	900	17,100	17,100
A11.3 nurse charge per month	900	17,100	17,100
A12 program management (on top from NHSO)	3,000	57,000	57,000
A13 Mobile phone call	180	3,420	3,420
A14 Mobile phone package	1130	14,400	14,400
A15Mobile phone cost (for pt who didn't have mobile phone, 6 in 19 and 2 for call center)	295	5,600	5,600
ToTal		2,278965	2,252,245
B. Patient costs (direct cost) B1 Visits to a health facility Indirect costs	1,800	34,200	34,200
B2 Absence from work (labor cost/day from Average income per month)	1,980	37,620	37,620
ToTal		71,820	71,820
C. Family costs (Indirect cost) 1.1 Transportation cost with patient			
1.2 Absence from work (labor cost/day from average income per month)	1,800 1,980	34,200 37,620	34,200 37,620
ToTal		71,820	71,820
D. Volunteer costs (direct cost)			
1.1 payment charge for volunteerDOT visits	1,800	-	34,200
ToTal		-	34,200
Total (A+B+C+D)		2,422,605	2,430,085

Table 11.2 The total cost of managing a TB patient to treatment completion between mobile phone& Non mobile intervention in non MDR group

Cost Analysis Direct cost A. Provider cost	unit cost per patient	Non MDR-TB gr (n=60)	
		Mobile(n=30)	Non Mobile(n=30)
		Total cost	Total cost
A1 Drug regimen 2HRZE(S) /4HR	2,380	71,400	71,400
A2 Material for Sputum Smears 6 times	360	10,800	10,800
A3 Material for Sputum Cultures 6 times	1,200	36,000	36,000
A4 Material for Sputum DST 1 time	100	3,000	3,000
A5 Material for Sputum for Identity NTM	350	10,500	10,500
A6 Specimen transportation 6 times	240	7,200	7,200
A7 Lab labour * AFB+C/S+ PCR+DST	230/mobile 263.3/non mobile	6,900	7,900
A8 BUN , Creatinine,SGOT,SGPT 2 times	440	13,200	13,200
A9 X-rays 2 times	160	4,800	4,800
A10 Program management at regional/provincial level(conference meeting and supervision)	5,380	174,900	174,900
A11 Program management (on top from NHSO)	800	24,000	24,000
A12 payment charge for nurse	200	6,000	6,000
A13 Mobile phone call 6 months	60	1,800	-
A14 Mobile phone package	80	2,400	-
A15 Mobile phone cost (for pt who didn't have mobile phone, 8 in 30)	187	5,600	-
ToTal		377,600	375,200
B. Patient costs (direct cost)			
B1 Visits to a health facility	480	14,400	14,400
Indirect costs			
B2 Absence from work	672	20,160	
(labor cost/day from income per month)			20,160
ToTal		34,560	34,560
C. Family costs (Indirect cost)			
1.1 Transportation cost with patient	480	14,400	14,400
1.2 Absence from work	672	20,160	20,160
(labor cost/day from income per month)			
ToTal		34,560	34,560
D. Volunteer costs (direct cost)			
1.1 DOT visits for collected sputum (on top from HHSO)	100	-	3,000
ToTal		--	3,000
Total (A+B+C+D)		446,720	447,320

Table 12 Average Total cost per patient to treatment completetion between mobile phone & non mobile phone intervention in MDR and non MDR TB group

Patient Group	Average Total cost / patient (baht)		p-value
	Mobile phone	Non Mobile phone	
MDR TB group	127,506.00	127,899.00	
Non MDR TB group	14,890.67	14,910.67	0.674

X^2 test for p- value

In table 12 the average total cost per patient of MDR and non MDR-TB with Mobile phone group was lower than the group that unused mobile phone only baht 393 in MDR-TB and baht 20 in non MDR-TB group. And the average total cost for cure was not different significant in both group respectively (p-value= 0.674)

Effectiveness of DOTS-Plus by using mobile phone was calculated as the average cost per patient treated successfully and found that cost effective ratio was -14.6 baht/patient treated successfully in MDR group and was -5.0 baht/patient treated successfully in non MDR group as in table 13. So these intervention showed the high of cost effectiveness.

Table 13 Cost effective analysis between mobile phone & non mobile phone intervention in MDR and non MDR TB group

Policy	Average cost/pt of Mobile phone gr	Average cost/pt of non Mobile phone gr	Patient treated successfully of Mobile phone gr	Patient treated successfully Of non Mobile phone gr	Cost effectiveness ratio (CE) baht/pt treated successfully
MDR TB gr	127,506.00	127899.00	1 คน	.73 คน	-14.6
Non MDR TB gr	14,890.67	14,910.67	1 คน	.96 คน	-5.0

Summary

From analysis result of experimental study in kind of True Experimental study (Randomized controlled trial) to compare effectiveness of TB patient care with MDR-TB between model 1 and model 2, it shows that

1.Model 2 could help the TB patient with positive disease sputum specimen to become negative within short period, that is, within the 1st month, with statistical significance at P< 0.001 in MDR-TB group . It helped to stop the epidemic of MDR-TB.

2.Model 2 could help to decrease failure rate or increase success rate with statistical significance at p= 0.0001 in MDR-TB group and p=0.047 in non MDR-TB group. And could be achieve key TB control program indicators as indicate by WHO.

3. Model 2 was effectiveness than Model1 (the CE ratios reflecting the cost benefits of both MDR and non MDR group in DOTS-Plus with mobile phone strategy arm were very low and in negative territory) And could be save budget of laboratory labor and transportation of specimens and pay for volunteers 1,000 baht/ person in the group with MDR-TB and 62.25 baht/person in the group with non MDR-TB.

CHAPTER 5

Discussion and Conclusion

Discussion

As the study result as above, it is found that DOTS-Plus and use of reminding phone made situation of MDR-TB in the northern area of Thailand had decreasing trend from 4.1 percents during April 2008 – September 2008 to be 1.8 percents during April 2009 – September 2009. Consequently, the implementation method is a method helping to resolve the problem of MDR-TB in the northern of Thailand from high rate of MDR-TB in the past to become the rate lower than Hot spot.

Especially, DOTS-Plus in Model 2, having reminding communication to the patient for medication every meal and coming to have physical examination and have sputum specimen examination, and receive drug continuously every month by using mobile phone auxiliary to effectiveness of treatment since it could increase success ratio to reach 100 percents. And it also could help to improve conversion rate in sputum specimen from positive to become negative in shorter time, that is, within the 1st month, it is in high level as 84.2 percents. When comparing to the model 1 that operation was conducted according to usual public health service system, accompanying with reminding for meditation from volunteer, it is found that conversion rate in the 1st month is only 57.9 percents. By the way, the reminding phone could help to improve behavior of the patients especially in MDR TB group as follow:

1) It helped to remind the patient to bring the sputum specimen for examining regularly with quality, that is, the patient of group of model 2 had result of sputum specimen examination by culturing fully in every month. This is different from the group of model 1 by observing in assessment result on cure rate and complete rate. If the result of sputum specimen examination is full, complete rate would be low but cure rate would be high.

2) It helped to improve behavior of cessation of meditation from misunderstanding that the symptom become well and the sputum specimen became negative and meditation was done regularly according to prescription of physician.

3) It helped to reduce forgetting to take medicine in each meal. For example, a patient in group of model 2 enjoying in working if there was no reminding phone, he might forget taking medicine for the last 6 months.

4) It helped to reduce behavior of omission of taking some medicine since the patient understood that he might feel no good when took such medicine. This causes effectiveness of meditation decreased down and it was found in the group of model 1, 1 person.

5) It helped to support intention and understanding on the reason of meditation for effectiveness of treatment outcome and this was found in most patients of the model 2.

6) It helped the patient to reduce the discremination and it was confidentiality for the patient live in the social usually. We can see this from the patient in group of model 2 where the patient went along to take medicine fully and had sputum examination fully, there was no failure of treatment while in usual model or model 1, the failure rate was 26.3 percents. In the sample of group of model 1, a patient followed up and paid attention by the officer so that the patient would take the medicine regularly by contacting to relatives and teacher in school to help to take care of her for meditation but the teacher expressed his intention to have the student stop attending the class and it made the student felt unhappy so that it effected to the treatment for this student was failed. This point is very important, that is, paying attention on feeling of patient. This is consistent to the study of Dr. Surasingh Wisarurat, a dentist who specializes in preventive medicine of Public Health Office, Chiang Mai [13], on use of mobile phone for TB patient care, showing that when the mobile phone is conducted to follow up the patient, the patients feel warm, not alone, no discremination by the social, and are encouraged to take care of themselves to become healthy.

7) it has high possibility to develop the process of use of remineing phone because about 80 percents of patients in the project have their own mobile phone and the expense of call center for communication to the patient also is not high, just about 500 baht per month by post pay and we can pay the incentive for staff at call center to communicate to patients as this project.

By total point of view, possibility of success of this project is so high since the treatment outcome in the patient without MDR-TB who taking medicine with DOT (not DOTS-Plus) only 6 months and number of medicine they took was not much and the side effect also was not much like the group of MDR-TB. Totally in the northern area, the

success rate of operation was only 72 percents [50], lower than level targeted by WHO. And when it is compared to study result on DOTS-Plus in several levels in various countries according to summary of analysis on Treatment of MDR -TB :TRC Experience (1980-2005) of Tuberculosis Centre Chennai[51],it is found that cure rate is in low level, averagely at 65 percents, lower than result of the model 2 and model 1 of this study. And when it is compared to the study of WHO at Philippines, Estonia, and Russia, on effectiveness of operation by using DOTS-Plus method, comparing the result between before and after using DOTS-Plus method [52-54], it is found that after using DOTS-Plus, the cure rate was increased in the level of 60-75% (The cure rate of the new patients are higher than the one of the patient who were treated before). The process of DOTS-Plus focuses on drug formula selection according to the result of MDR-TB of each patient and this result is similar to the result of this study on model 1 of MDR TB group even it is lower than the model 2 but it is worth for WHO to apply for further operation.

The CE ratios reflecting the cost benefits of both MDR and non MDR group in DOTS-Plus with mobile phone strategy arm were very low and in negative territory. If mobile phone is to be used. It should be used in MDR group since this group had more negativeity of CE ratio than non MDR group.

Anyway, the different costs between the group with mobile phone and without mobile phone are cost of laboratory labor, transportation of specimens and for volunteers, where the cost of Laboratory labor and pay for volunteers in the group without mobile phone are higher than the group with mobile phone 38,095.00 baht or 4.6 times of cost in the group with mobile phone in MDR-TB group and was double in the group with non MDR-TB .

In such case, if we apply the method 2 (DOTS-plus with mobile phone), we will save budget of examination and transportation of specimens and pay for volunteers 1,000 baht/ person in the group with MDR-TB and 62.25 baht/person in the group with non MDR-TB.

Factors influencing to success of this project as DOTS-plus

1. **Political commitment** of the Ministry of public Health.
2. **Coordination** : –It depends on the area with good coordinator. In this project, the pay is motivation.

3. Laboratory :- requires TB culture and Identify for mycobacterium tuberculosis, and TB drug sensitivity test (DST) with standardization, where in this project, TB Center Zone 10 handled quickly within 1 month after receipt of specimens.

4. Treatment strategy :- The physician has to have the technique ensuring that the patients will receive the drug and the patients have to come to receive the drug at the hospital near their home continuously for at least 18 months. And the physician has to know side effect of each kind of drug used for treatment for effective attendance to the patients. (In this study, the patients were facilitated to take the drug regularly by using mobile phone to give counseling on taking drug every meal.)

5. Information systems and data management :-To run DOT-Plus well, it requires the efficient data system able to use to follow treatment of each person.(In this study, the data system was set for drug resistance monitoring and following up provision of attendance and treatment, able to reply the study result if the project can achieve reduction of multi-drug resistance)

Recommendation

From reduction of prevalence rate of MDR-TB from 4.1% in year 2008 to be 1.8% in year 2009, or from 87 persons to be 38 persons, this is deemed that it could help to save budget of government for treatment about 5,992,782 baht, and also could stop epidemic of MDR-TB too. If there is separate investment, excluding the cost of drug from National Health Seculity Organization(NHSO) funds for treatment for about 38-40 persons expected that they still remain in the area about 1,508,702.00 baht/year (Total cost of managing MDR-TB patients to completion –Drug cost) continuously in order to fund total management cost except the drug cost, it will be able to help stop epidemic of MDR-TB in the northern area.

Conclusion

In summary ,This paper describes our experiences with DOTS-Plus by mobile phone and the successful outcome suggests that DOTS-Plus by mobile phone is feasible ,affordable and cost effectiveness to extend application of process to area having high MDR TB prevalence

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Appendices

Appendix A

ข้อมูลสำหรับกลุ่มประชากรหรือผู้มีส่วนร่วมในการวิจัย

ชื่อโครงการวิจัย

การศึกษาเปรียบเทียบต้นทุนและประสิทธิภาพของการดูแลรักษาผู้ป่วยวัณโรคระหว่างการใช้ระบบบริการสาธารณสุข และ การใช้ระบบบริการสาธารณสุขร่วมกับ การสื่อสารด้วยโทรศัพท์มือถือ ภายใต้ระบบ DOTS-Plus ในเขตพื้นที่ภาคเหนือตอนบน

ชื่อผู้วิจัยนางสาวปิยะดา คุณาวารักษ์

ตำแหน่ง นักวิชาการสาธารณสุขระดับชำนาญการพิเศษ

สถานที่ติดต่อผู้วิจัย

(ที่ทำงาน) สำนักงานป้องกันควบคุมโรคที่ 10 เชียงใหม่

(ที่บ้าน) 24 ถนนสันป่าข่อย ตำบลวัดเกต อำเภอเมือง จังหวัดเชียงใหม่

โทรศัพท์ (ที่ทำงาน) 053-140774-6 ต่อ 119 โทรศัพท์ที่บ้าน 053-303065

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1. ขอเรียนเชิญท่านเข้าร่วมในการวิจัยก่อนที่ท่านจะตัดสินใจเข้าร่วมในการวิจัย มีความจำเป็นที่ท่านควรทำความเข้าใจว่างานวิจัยนี้ทำเพราะเหตุใด และเกี่ยวข้องกับอะไร กรุณาใช้เวลาในการอ่านข้อมูลต่อไปนี้อย่างละเอียดรอบคอบ และสอบถามข้อมูลเพิ่มเติมหรือข้อมูลที่ไม่ชัดเจนได้ตลอดเวลา

โครงการนี้เกี่ยวข้องกับการวิจัยคือ

โครงการนี้ดำเนินการในพื้นที่ภาคเหนือตอนบน เนื่องจากในพื้นที่ภาคเหนือตอนบน ซึ่งหมายถึง พื้นที่จังหวัด เชียงใหม่ ลำพูน ลำปาง พะเยา เชียงราย แพร่ น่าน และแม่ฮ่องสอน เป็นพื้นที่ที่มีอัตราการป่วยด้วยวัณโรคสูง และผู้ป่วยเมื่อป่วยเป็นวัณโรคแล้วก็พบว่ามีการรักษาให้หายขาดได้ต่ำ คือสามารถรักษาให้หายขาดได้เพียงร้อยละ 72 ซึ่งต่ำกว่าเป้าหมายที่ตั้งไว้ คือ ที่ร้อยละ 85 ทั้งนี้อาจเนื่องมาจาก ผู้ป่วยมีการติดเชื้อวัณโรคที่ดื้อยารักษาวัณโรคมากกว่าขนาน ซึ่งแต่เดิมนั้นแพทย์ผู้รักษายังไม่ทราบว่าผู้ป่วยมีการติดเชื้อวัณโรคที่ดื้อยาก่อนการให้การรักษา หรือผู้ป่วยอาจติดเชื้อวัณโรคปลอม ซึ่งทำให้การรักษาไม่หายขาด หรือผู้ป่วยอาจมีการป่วยร่วมกับโรคอื่นๆ เช่น โรคเบาหวาน โรคความดันโลหิตสูง หรือโรคหัวใจและหลอดเลือด หรือผู้ป่วยวัณโรคที่ติดเชื้อเอดส์มาเข้ารับบริการรักษาช้าไปทำให้ต้องเสียชีวิตลง ซึ่งจะส่งผลให้เกิด

การตายด้วยวัณโรคสูงตามมาด้วย ดังนั้นโครงการนี้จึงต้องการทราบวิธีการดูแลรักษาผู้ป่วยวัณโรคแบบไหนที่จะส่งผลให้ผู้ป่วยวัณโรคได้รับการรักษาอย่างมีคุณภาพ คือ ผู้ป่วยหายขาดจากการเป็นผู้ป่วยเป็นวัณโรคไม่มีเชื้อ อวัณโรคในเสมหะที่จะแพร่กระจายให้คนในชุมชน ทั้งนี้ เนื่องจากที่ผ่านมาผู้ป่วยมักจะทานยาไม่ครบ ทำให้เชื้อเกิดการดื้อยา และไม่หาย โดยอาจลืมทาน หรือผู้ป่วยอาจไม่ให้ความสำคัญต่อการกินยา เช่น บางครั้งหากไม่มีอาการ ก็ละเลย ไม่ให้ความสำคัญต่อการกินยาให้สม่ำเสมอทุกมื้อตามแพทย์สั่ง

วัตถุประสงค์ ของโครงการนี้ คือ หาวิธีให้การดูแลรักษาผู้ป่วยวัณโรคทั้งที่ดื้อยารักษาวัณโรคและไม่มีการดื้อยาวัณโรค ที่มีประสิทธิภาพ โดย ศึกษาทดลองว่า หากมีการโทรศัพท์เตือนและให้คำปรึกษาในการกินยาทุกมื้อแก่ผู้ป่วยวัณโรคแล้ว จะช่วยทำให้ผู้ป่วยวัณโรคทานยาครบ และจะส่งผลต่อการรักษาหายขาดจากวัณโรคเพิ่มสูงขึ้น ซึ่งจะลดปัญหาการแพร่ระบาดของผู้ป่วยวัณโรคที่ดื้อยาวัณโรคได้อย่างคุ้มค่า

กลุ่มประชากร หรือผู้มีส่วนร่วมในโครงการวิจัยนี้ คือ ผู้ที่มีอาการสงสัยเป็นวัณโรค มารับการตรวจที่โรงพยาบาลของรัฐในพื้นที่จังหวัดเชียงใหม่ ลำพูน พะเยา ลำปาง เชียงราย แม่ฮ่องสอน แพร่ และ น่าน และได้รับการตรวจเสมหะว่าพบเชื้อวัณโรคโดยวิธีเพาะเชื้อและตรวจแยกเชื้อว่าเป็นวัณโรคปอด โดยมีเกณฑ์คัดเข้าโครงการ ดังนี้

เกณฑ์คัดเข้าโครงการ

1) เป็นผู้ป่วยวัณโรคปอดทั้งดื้อยาหรือไม่ดื้อยาวัณโรค
2) กรณีดื้อยาวัณโรคแบบ ดื้อยาหลายขนาน ต้องไม่เคยได้รับการรักษา ด้วยสูตรยารักษาวัณโรคที่ดื้อยาหลาย ขนาน

2.1) ได้รับการตรวจแยก ว่าเป็นวัณโรคปอด (Mycobacterium Tuberculosis)

2.2) ได้รับการตรวจเลือดหาเชื้อเอดส์

2.3) ได้รับการตรวจเลือดเพื่อดู สภาพ การทำงานของ ตับ และ ไต ซึ่งต้องมีค่าไม่เกิน 2 เท่า ของค่าปกติ

2.4) อายุตั้งแต่15 ปีขึ้นไป

เกณฑ์คัดออกโครงการ

1) เป็นผู้อยู่ระหว่างการตั้งครรภ์หรือ เลี้ยงลูกด้วยนม
2) มีประวัติเป็นลมชัก (epilepsy)

3) มีประวัติเป็นผู้ติดเหล้า(Alcoholism)

4) ไม่สามารถพูดจาโต้ตอบกับผู้วิจัยได้เข้าใจ

5) มีการดื้ อยา ไอโซไนอาซิดและ ไรแฟมพิซินร่วมกับ กานามัยซิน โอฟรอกซาซิน ไพราซินาไมด์ และ พีเอ เอส

6) ไม่สามารถเข้ารับการรักษา โดยมารับการฉีดยาทุกวันเป็นเวลา 3 เดือนนับจากเริ่มรักษา และไม่สามารถมารับการตรวจติดตามทุกเดือนได้จนครบกำหนดการรักษา

เกณฑ์การให้เลิกจาก โครงการ

1) อาสาสมัครขอถอนตัวออกจากการรักษา

2) อาสาสมัครเสียชีวิต

3) อาสาสมัครขอโอนย้ายไปที่อื่น ขาดการรักษา โดยไม่สามารถติดตามได้

และในโครงการนี้ จะรับผู้ป่วยเข้าร่วมโครงการทั้ งหมด 100 คน เป็นกลุ่มที่ไม่ดื้ อยาวัณโรค 60 คน และเป็นกลุ่มที่ดื้ อยาวัณโรคหลายขนาน40 คน

ทั้ งนี้ เนื่องจากท่านเป็นผู้มีคุณสมบัติตามเกณฑ์ของโครงการวิจัย ทางโครงการจึงขอเชิญท่าน เข้าร่วมโครงการวิจัย โดยที่โครงการวิจัยนี้ จะแบ่งกลุ่มผู้เข้าร่วมวิจัยเป็น 4 กลุ่ม คือ

กลุ่มที่ 1 คือ กลุ่มที่ดื้ อยาวัณโรคที่ไม่ได้รับโทรศัพท์มือถือ ซึ่งจะได้รับการรักษาตามระบบปกติของ โรงพยาบาล แต่ ไม่มีการโทรเตือนให้กินยา

กลุ่มที่ 2 คือ กลุ่มที่ดื้ อยาวัณโรคที่ได้รับโทรศัพท์มือถือ ซึ่งจะได้รับการรักษาตามระบบปกติของโรงพยาบาล แต่ มีการโทรเตือนให้กินยาทุกมื้ อ ซึ่งผู้ป่วยสามารถได้รับคำปรึกษาอย่างใกล้ชิดกรณีมีปัญหาด้านการกินยา

กลุ่มที่ 3 คือ กลุ่มที่ไม่ดื้ อยา ที่ไม่ได้รับโทรศัพท์มือถือ ซึ่งจะได้รับการรักษาตามระบบปกติของโรงพยาบาล ไม่มีการโทรเตือนให้กินยา

กลุ่มที่ 4 คือ กลุ่มที่ไม่ดื้ อยา ที่ได้รับโทรศัพท์มือถือ ซึ่งจะได้รับการรักษาตามระบบปกติของโรงพยาบาล แต่ มีการโทรเตือนให้กินยาทุกมื้ อ

ในกระบวนการวิจัยดังกล่าวผู้เข้าร่วมวิจัย โปรดทราบว่า ผู้ดำเนินการโครงการวิจัยนี้ คือ นางสาวปิยะดา คุณาวารักษ์ นักวิจัยจากสำนักงานป้องกันควบคุมโรคที่ 10 เชียงใหม่ ได้จัดทำโครงการวิจัยร่วมกับโรงพยาบาลของรัฐในเขต ภาคเหนือตอนบน ซึ่งจะมีขั้ นตอนในการดำเนินการดังนี้

1 ทางโรงพยาบาลของรัฐในเขตภาคเหนือตอนบน จะเป็นผู้คัดกรองหาผู้มีคุณสมบัติตามเกณฑ์ที่กล่าวมา เข้าโครงการ

2 เมื่อพบว่าผู้ป่วยท่านใดมีคุณสมบัติครบตามที่กล่าวมา เจ้าหน้าที่หรือพยาบาลที่รับผิดชอบการดูแลผู้ป่วยวัณโรคจะเป็นผู้ให้เอกสารข้อมูลของโครงการและคำอธิบายแก่ผู้ป่วยที่มีคุณสมบัติและเชิญผู้ป่วยเข้าร่วมโครงการ

3 เมื่อผู้ป่วยตกลงเข้าร่วมโครงการ เจ้าหน้าที่หรือพยาบาลที่รับผิดชอบของโรงพยาบาลจะนำเอกสารใบยินยอมเข้าร่วมโครงการ ให้ลงนามเข้าร่วมโครงการ

4 กรณีที่ผู้ป่วยที่มีคุณสมบัติได้ลงนามยินยอมเข้าร่วมโครงการแล้ว ผู้ป่วยจะได้รับการสัมภาษณ์ตรวจร่างกายตามประวัติข้อมูลทั่วไปและข้อมูลสุขภาพของผู้ป่วย และหากผู้ป่วยถูกเลือกเป็นกลุ่มที่ได้รับโทรศัพท์ ซึ่งจะถูกเลือกโดยวิธีการสุ่มจากผู้ดำเนินการวิจัย ก็จะได้รับโทรศัพท์ พร้อมซิม พร้อมได้รับการสอนวิธีการใช้โทรศัพท์ และแจ้งให้ผู้ป่วยทราบว่า ผู้ป่วยจะได้รับการโทรมาแจ้งเตือนให้กินยาตามเบอร์ที่ให้ และหากผู้ป่วยต้องการคำปรึกษาใดๆในด้านการกินยาสามารถขอคำปรึกษาได้ ทั้งนี้ ผู้ป่วยที่เข้าร่วมโครงการทุกคนจะได้รับการดูแลรักษาที่เหมือนกันดังนี้

* ผู้เข้าร่วมโครงการต้องเก็บเสมหะมาให้เจ้าหน้าที่โรงพยาบาลที่รับผิดชอบดูแล มาตรวจหาเชื้อวัณโรคทุกเดือน จนครบการรักษา กรณีดื้อยา ต้องรักษาครบ18 เดือน กรณีไม่มีการดื้อยาต้องรักษา ครบ 6 เดือน ทั้งนี้ อยู่ในการพิจารณาของแพทย์ที่ทำการรักษา
* ผู้เข้าร่วมโครงการจะได้รับการเอ็กซเรย์ปอดทุก6 เดือน จนครบการรักษา
* ผู้เข้าร่วมโครงการจะได้รับการเจาะเลือดตรวจ ประมาณ2 ช้อนโต๊ะ เพื่อดูสภาพการทำงานของตับ และไต ทุก 3 เดือน จนครบการรักษา
* ผู้เข้าร่วมโครงการ จะต้องมารับยาที่โรงพยาบาลทุก1 เดือนพร้อมรับสมุดบันทึกกำกับการกินยาและ นำสมุดบันทึกมาโรงพยาบาลทุกครั้งเมื่อมารับยาทุกเดือนเพื่อตรวจสอบการรับยาและกินยา
* กรณีที่ผู้เข้าร่วมโครงการเป็นผู้ป่วยที่ดื้อยาวัณโรค ท่านจะต้องมารับยาที่โรงพยาบาลทั่วไป หรือโรงพยาบาลศูนย์ในจังหวัดที่ที่ท่านอาศัยอยู่ทุกเดือน เพื่อแพทย์จะได้ให้การดูแลอย่างใกล้ชิด และ ต้องไปรับการฉีดยาอาทิตย์ละ 5 วัน เป็นเวลา 6 เดือน โดยสามารถเลือกสถานบริการใกล้บ้านซึ่งอาจจะเป็นโรงพยาบาลชุมชน หรือ สถานีอนามัยใกล้บ้านท่านเป็นผู้ฉีดยาให้

กรณีที่การคัดกรองผู้มีส่วนร่วมในการวิจัย ซึ่งพบว่าไม่มีคุณสมบัติเข้าร่วมโครงการได้ผู้ป่วยดังกล่าวจะได้รับการรักษาตามระบบปกติของโรงพยาบาลทุกประการ

ในกระบวนการรักษาทั้งหมด นี้ขึ้นอยู่กับความเห็นชอบจากแพทย์ผู้ดูแลรักษา อันตรายหรือความเสี่ยง ที่อาจเกิดขึ้นสำหรับผู้เข้าร่วมโครงการ นั้น กล่าวได้ว่า จะเป็นความเสี่ยงต่อการแพ้ยาที่รักษา ซึ่งขอเรียนให้ท่านทราบว่า ยาที่ใช้ในการรักษาในโครงการนี้ เป็นยาที่มีคุณภาพ ขึ้น

ทะเบียนแล้ว และเบิกจากระบบของโรงพยาบาล ซึ่งได้รับการสนับสนุนจากสำนักงานประกันสุขภาพแห่งชาติ ทั้งนี้ ในการดูแลรักษาท่านด้วยยารักษาวัณโรคที่กล่าวมาข้างต้น ยาบางตัวอาจทำให้เกิดอาการข้างเคียงหรือแพ้ยา เช่น ผื่นแดง, คัน, เหน็บชา, เวียนศีรษะ, นอนไม่หลับ, คลื่นไส้อาเจียน, ปวดตามข้อ หรือตามัว หรือยาบางตัวมีผลต่อการทำงานของไต กรณีที่มีอาการข้างเคียง จะมีการปรับขนาดยา ซึ่งแพทย์จะดูแลอย่างใกล้ชิดและพิจารณาแก้ไขในแต่ละกลุ่มอาการ ส่วนความเสี่ยงอีกประการคือ การรักษาและไม่หายขาด ซึ่งอาจเป็นสาเหตุจากชนิดของเชื้อ ซึ่งแพทย์จะพิจารณาการให้การรักษาต่อไป

ขอเรียนให้ท่านทราบว่า การเข้าร่วมเป็นกลุ่มประชากรหรือผู้มีส่วนร่วมในการวิจัยเป็นโดยสมัครใจและสามารถปฏิเสธที่จะเข้าร่วมหรือถอนตัวจากการวิจัยได้ทุกขณะ โดยไม่ต้องให้เหตุผลและไม่สูญเสียประโยชน์ที่พึงได้รับ กล่าวคือ จะไม่มีผลกระทบต่อการดูแลรักษาใดๆ ที่ท่านพึงได้รับในระบบปกติ

หากท่านมีข้อสงสัยให้สอบถามเพิ่มเติมได้โดยสามารถติดต่อผู้วิจัยได้ตลอดเวลาตามชื่อและเบอร์โทรศัพท์ที่ระบุข้างต้น และหากผู้วิจัยมีข้อมูลเพิ่มเติมที่เป็นประโยชน์หรือโทษเกี่ยวกับการวิจัย ผู้วิจัยจะแจ้งให้ท่านทราบอย่างรวดเร็ว

ข้อมูล ที่เกี่ยวข้องกับท่านจะถูกเก็บเป็นความลับ หากมีการเสนอผลการวิจัย จะเสนอเป็นภาพรวม ข้อมูลใดที่สามารถระบุถึงตัวท่านได้จะไม่ปรากฏในรายงาน

ทั้งนี้ ขอเรียนให้ท่านทราบว่า โครงการนี้ จะมีเงินชดเชย ค่าเดินทางมารับการ ตรวจรักษาที่โรงพยาบาลศูนย์ หรือ โรงพยาบาลทั่วไป ให้แก่ท่านทุกเดือนๆละ 100 บาท เฉพาะกรณีที่อาสาสมัครผู้เข้าร่วมโครงการที่มีผลเสมหะพบว่าดื้อยา หลายขนาน นอกเหนือจากการที่ท่านจะได้รับการรักษาโดยไม่เสียค่าใช้จ่าย ค่ายา และค่าตรวจเลือด ส่วนท่านที่ได้รับการสุ่มว่าได้รับโทรศัพท์เตือนให้กินยา จะได้รับโทรศัพท์เคลื่อนที่ 1 เครื่องพร้อม ซิมโทรนาน 1 ปี สำหรับรับโทรศัพท์ เพื่อเจ้าหน้าที่จะคอยเตือนให้ท่านไปฉีดยา และกินยาอย่างสม่ำเสมอ

สุดท้ายของโครงการนี้"หากท่านไม่ได้รับการปฏิบัติตามข้อมูลดังกล่าวสามารถร้องเรียนได้ที่ คณะกรรมการพิจารณาจริยธรรมการวิจัยในคน กลุ่มสหสถาบัน ชุดที่ 1 จุฬาลงกรณ์มหาวิทยาลัย ชั้น4 อาคารสถาบัน 2 ซอยจุฬาลงกรณ์ 62 ถนนพญาไท เขตปทุมวัน กรุงเทพฯ 10330 โทรศัพท์ 0-2218-8147 โทรสาร 0-2218-8147

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หนังสือแสดงความยินยอมเข้าร่วมการวิจัย

ทำที่.....
วันที่.....เดือน.....พ.ศ. .....

เลขที่ ประชากรตัวอย่างหรือผู้มีส่วนร่วมในการวิจัย.....

ข้าพเจ้า ซึ่งได้ลงนามท้ายหนังสือนี้ ขอแสดงความยินยอมเข้าร่วมโครงการวิจัย
ชื่อโครงการวิจัย การศึกษาเปรียบเทียบต้นทุนและประสิทธิภาพของการดูแลรักษาผู้ป่วยวัณโรคระหว่างการใช้ระบบบริการสาธารณสุข และ การใชระบบบริการสาธารณสุขร่วมกับ การสื่อสารด้วยโทรศัพท์มือถือ ภายใต้ระบบ DOTS-Plus ในเขตพื้นที่ภาคเหนือตอนบน
ชื่อผู้วิจัย... นางสาวปิยะดา คุณาวารักษ์
ที่อยู่ที่ติดต่อ 24 ถนนสันป่าข่อย ตำบลวัดเกต อำเภอเมือง จังหวัดเชียงใหม่
โทรศัพท์ 0864210116

ข้าพเจ้า ได้รับทราบรายละเอียดเกี่ยวกับที่มาและวัตถุประสงค์ในการทำวิจัย รายละเอียดขั้นตอนต่างๆ ที่จะต้องปฏิบัติหรือได้รับการปฏิบัติ ความเสี่ยงอันตราย และประโยชน์ซึ่งจะเกิดขึ้นจากการวิจัยเรื่องนี้ โดยได้อ่านรายละเอียดในเอกสารชี้แจงผู้เข้าร่วมการวิจัยโดยตลอด และได้รับคำอธิบายจากผู้วิจัย จนเข้าใจเป็นอย่างดีแล้ว

ข้าพเจ้าจึงสมัครใจเข้าร่วมในโครงการวิจัยนี้ ตามที่ระบุไว้ในเอกสารชี้แจงผู้เข้าร่วมการวิจัย โดยข้าพเจ้ายินยอม ให้นำเสมหะไปตรวจเพื่อหาการดื้อยาของเชื้อวัณโรค ให้สัมภาษณ์ข้อมูลตามแบบสอบถาม และนำเสมหะมาตรวจทุก 1 เดือน พร้อมให้แพทย์ตรวจร่างกายตรวจเลือดทุก 3 เดือน เอ็กเรย์ปอด ทุก 6 เดือนและมารับยาทุกเดือนเป็นระยะเวลา 18 เดือนกรณีที่เสมหะท่านตรวจพบเชื้อดื้อยารักษาวัณโรค หรือเป็นระยะเวลา 6 เดือนกรณีที่เสมหะของท่านไม่พบเชื้อที่ดื้อยาวัณโรค

ข้าพเจ้ามีสิทธิถอนตัวออกจากการวิจัยเมื่อใดก็ได้ตามความประสงค์ โดยไม่ต้องแจ้งเหตุผล ซึ่งการถอนตัวออกจากการวิจัยนั้น จะไม่มีผลกระทบในทางใดๆ ต่อข้าพเจ้าทั้งสิ้น กล่าวคือท่านจะไม่สูญเสียประโยชน์ที่พึงได้รับและไม่มีผลกระทบต่อการดูแลรักษาใดๆที่ท่านพึงได้รับ ตามระบบปกติ

ข้าพเจ้าได้รับคำรับรองว่า ผู้วิจัยจะปฏิบัติต่อข้าพเจ้าตามข้อมูลที่ระบุไว้ในเอกสารชี้แจงผู้เข้าร่วมการวิจัย และข้อมูลใดๆ ที่เกี่ยวข้องกับข้าพเจ้า ผู้วิจัยจะเก็บรักษาเป็นความลับ โดยจะนำเสนอข้อมูลการวิจัยเป็นภาพรวมเท่านั้น ไม่มีข้อมูลใดในการรายงานที่จะนำไปสู่การระบุตัวข้าพเจ้า

หากข้าพเจ้าไม่ได้รับการปฏิบัติตรงตามที่ได้ระบุไว้ในเอกสารชี้ แจงผู้เข้าร่วมการวิจัย ข้าพเจ้าสามารถร้องเรียนได้ที่คณะกรรมการพิจารณาจริยธรรมการวิจัยในคน กลุ่มสหสถาบัน ชุดที่ 1 จุฬาลงกรณ์มหาวิทยาลัย ชั้น 4 อาคารสถาบัน 2 ซอยจุฬาลงกรณ์ 62 ถนนพญาไท เขตปทุมวัน กรุงเทพฯ 10330 โทรศัพท์ 0-2218-8147 โทรสาร 0-2218-8147 E-mail: eccu@chula.ac.th

ข้าพเจ้าได้ลงลายมือชื่อไว้เป็นสำคัญต่อหน้าพยาน ทั้งนี้ ข้าพเจ้าได้รับสำเนาเอกสารชี้ แจงผู้เข้าร่วมการวิจัย และสำเนาหนังสือแสดงความยินยอมไว้แล้ว

ทั้งนี้ ผู้วิจัย ได้ให้ข้อมูลแก่ผู้มีส่วนร่วมในการวิจัยนี้ แล้ว

ลงชื่อ .....
(.. นางสาวปิยะดา คุณาวรารักษ์..)
ผู้วิจัยหลัก

ลงชื่อ .....
(.....)
ผู้มีส่วนร่วมในการวิจัย

ลงชื่อ .....
(.....)
พยาน

Appendix B

Form 1 Patient History

Cost-Cost effectiveness ;A comparative study of TB and MDR TB case management with Health volunteer & Health facility base model versus Health facility base & mobile phone communication by DOTS-PLUS strategy in upper north of Thailand

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1.Patient's name-surname ....ID.cardNo..... .

2.TB.No .....MDR-TB No .....

3. HN.no.....Sex ☐ Male ☐Female Age .....

4. Occupation..specify.....

5. Marietal status.. ☐couple ☐single ☐widow ☐divorce

6. Education ☐ no education ☐ Primary school

☐ Secondary school ☐ Vocational

☐ Bachelor's degree ☐ Master's degree ☐ other.....

7. Adress .....Mu..... .....Tumbon.....Amphure.....

Province..... ☐ municipal ☐ out municipal

8. Work place Adress.....

9.Home Tel..... Office Tel.....

Mobile phone ....

Illness History

10.Did you have Diabetis

☐ Yes ☐ No year of ill.....

11. Did you have HIV infection

☐ Yes ☐ No Year of infection.....

12. If you have HIV infection , : Did you recieved ART ?

☐ Yes ☐ No Year of given ART.....

13. Did you ever been receive TB drug?

☐ Yes ☐ No

Year of given TB drug..... Hospital of TB drug given.....

14. If you have HIV infection , Did you ever been receive TB drug ?

☐ Yes ☐ No Year of given TB drug.....

15. Did you smoke?

☐ Yes ☐ No

16. Did you Drink alcohol?

☐ Yes ☐ No

17. If you drink alcohol , How frequency you have?

☐ every day ☐ 2-3 time/week ☐ other……

18. Did you ever been used IVD ?

☐ Yes ☐ No

19. Did you ever been have drug allergy ?

☐ Yes ☐ No

If you ever been have , which drug……

20. Did you have any symptom ?. when you came to hospital.

☐ caugh ☐ caugh with symptom ☐ sputum with blood/swamp

☐ chest pain ☐ tried/tote ☐ fever ☐ other specify……

How long of symptom? …… (week/month/year)

21. How many person in your family ?.....person

22. Did your family have TB patient ?

☐ Yes ☐ No ☐ other specify……

23. Did your family ever been have TB patient.?

☐ Yes ☐ No ☐ other specify……

24. How many hour from your home and hospital.? Specify Hour/ Minute

25. Cost for transportation from your home to hospital. Specify real cost……baht

26. Did the patient have accompany to hospital ☐ Yes ☐ No ☐ other ……

27. The accompany of patient was in family or from nabour ☐ family ☐ nabour……

27. Income of patient per month…Specify real cost ……baht.

28. Income of patient per month…Specify real cost ……baht.

Reporter.Name.....

Report Date ……/……/……

FORM 2 แบบสรุปการสิ้นสุดการศึกษาของผู้ป่วย
ในโครงการวิจัย เรื่องประสิทธิภาพของการดูแลรักษาผู้ป่วยวัณโรคที่ดื้อยารักษาวัณโรคอย่างน้อย2 ขนาน ภายใต้ระบบ DOTS ในเขตภาคเหนือตอนบน

---

1. ชื่อผู้ป่วย.....นามสกุล
.....

2. ชื่อโรงพยาบาลที่รับการรักษา . รพท
.....
รพช.....

3. ผลการสิ้นสุดการรักษาในโครงการ

3.1 ☐ ขอยุติการเข้าร่วมโครงการ ด้วยสาเหตุ☐ DEAD
☐ Transfer out
☐ อื่นๆ ระบุ .....

3.2 ☐ รักษาครบ ผลการรักษา ☐ Cure
☐ Success
☐ Complete
☐ Failure
☐ Relape

3.3 ☐ ตาย ด้วยสาเหตุ ☐ TB Dead จากสาเหตุ.....
☐ Non-TB Dead จากสาเหตุ.....

ผู้บันทึก.....
วดป ที่บันทึก .....

แบบฟอร์มที่ 3

แบบรายงานการเบิกยาต้านวัณโรค MDR-TB

โครงการวิจัยเรื่อง ประสิทธิผลของการดูแลรักษาผู้ป่วยวัณโรคที่ดื้อยาวัณโรคอย่างน้อย2 ขนาน ภายใต้ระบบ DOTS ในเขตภาคเหนือตอนบน

---

1. **วัน เดือน ปี ที่ขอเบิก.....ชื่อโรงพยาบาล .....**

2. **ชื่อ-สกุล ผู้ป่วย.....**HN……**น้ำหนัก.....กก.**

3. **การรักษา** MDR-TB

3.1 **กรณีผู้ป่วยเริ่มยาครั้งแรก**

สูตรยาเริ่มต้น.....

3.2 **กรณีเบิกยาต่อเนื่อง**

สูตรยาที่ใช้ในปัจจุบัน.....

รายการยาที่เบิก (ควรเบิกสำหรับใช้ในระยะเวลาไม่เกิน 4 เดือน)

Ofloxacin (200)	จำนวน.....x 100's
Ofloxacin (100)	จำนวน.....x 100's
PAS (1 gm)	จำนวน.....x 1000's
Ethionamide (250)	จำนวน.....x 100's
Kanamycin 1 gm. Inj	จำนวน.....vials
D-cycloserine (250)	จำนวน.....x 100's (เบิกได้เฉพาะกรณีจำเป็นเนื่องจากไม่อยู่ในguideline)

ลงชื่อ .....ผู้รายงาน

(.....)

ตำแหน่ง .....

หมายเหตุ : 1. แบบฟอร์มนี้ใช้ประกอบกับใบเบิกยาและเวชภัณฑ์ สำนักงานป้องกันควบคุมโรคที่10 แบบรายงาน 1 ฉบับ ต่อผู้ป่วย 1 ราย

DOTS-Plus Health facility (Form 4.1)

Patient name ....Project ID.No……..…… .TB.No……..……
MDR-TB no ……..
Define sample case control Hospital name……..

TB Drug given by regimen……

m/y	time	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	wt	AFB	X-ray
May52	Day																																		
	Noon																																		
	nigth																																		
Jun52	Day																																		
	Noon																																		
	nigth																																		
Jul-52	Day																																		
	Noon																																		
	nigth																																		
Aug-52	Day																																		
	Noon																																		
	nigth																																		
Sept52	Day																																		
	Noon																																		
	nigth																																		
Oct-52	Day																																		
	Noon																																		
	nigth																																		
Nov-52	Day																																		
	Noon																																		
	nigth																																		
Dec-52	Day																																		
	Noon																																		
	nigth																																		
Jan-53	Day																																		
	Noon																																		
	nigth																																		
Feb-53	Day																																		
	Noon																																		
	nigth																																		
Mar-53	Day																																		
	Noon																																		
	nigth																																		
Apr-53	Day																																		
	Noon																																		
	nigth																																		

Note : Method to correct data : O=Directly observed N= not supervised X= Not given drug

DOTS-Plus Health facility (Form 4.2)

Patient name .....**Project ID. No**..... .**TB. No**..... **MDR-TB no** .....

Define sample **case** **control** **Hospital name**.....

Drug used with dose in each month by Regimen .....

d/m/y	H	R	Z	E	S	Km	Am	Cm	FQ	Pto /Eto	Cs	PAS	อื่นๆ	patient 's symptom				comment
														better	worse	stable	other	
May-52																		
Jun-52																		
Jul-52																		
Aug-52																		
Sept52																		
Oct-52																		
Nov-52																		
Dec-52																		
Jan-53																		
Feb-53																		
Mar-53																		
Apr-53																		
May-53																		
Jun-53																		
Jul-53																		
Aug-53																		
Sept53																		
Oct-53																		
Nov-53																		
Dec-53																		
Jan-54																		
Feb-54																		
Mar-54																		
Apr-54																		
May-54																		
Jun-54																		

Name of data recorder .....

DOTS-Plus Health facility (Form 4.3)

Patient name ..... **..Project ID.No**..... **.TB.No**..... **MDR-TB no** .....

Define sample **case** **control** **Hospital name**.....

Side effect record

D/M/Y	beriberi	rash	Psycotic	anxiety	convulse	headache	not sleep	nausia	anomxia	Peptic	arthrogia	deceived	colur blindness	HT	pulse	respiration	other	How to treat
May-52																		
Jun-52																		
Jul-52																		
Aug-52																		
Sept52																		
Oct-52																		
Nov-52																		
Dec-52																		
Jan-53																		
Feb-53																		
Mar-53																		
Apr-53																		
May-53																		
Jun-53																		
Jul-53																		
Aug-53																		
Sept53																		
Oct-53																		
Nov-53																		
Dec-53																		
Jan-54																		
Feb-54																		
Mar-54																		
Apr-54																		
May-54																		
Jun-54																		

Drug regimen used ..... Any adjust regimen ☐ No ☐ Yes Which regimen.....

DOTS-Plus Health facility (Form 4.4)

ชื่อ-สกุลผู้ป่วย .....**Project ID.No**..... .....**.TB.No**..... **MDR-TB no** ....

ประเภทกลุ่มตัวอย่าง กลุ่มศึกษา กลุ่มควบคุม ชื่อ รพ.....

Summarize of treatment follow-up

Symptom show	Day 0 (Base line)	Duration of treatment				
		Month 9	Month 12	Month 15	Month 18	End of treatment
Body wt						
Temparature						
RR						
Dyspnea sign						
Symptom**						
Direct smear						
TB culture						
DST						
CXR						
ADR ระบุ						
Lab ***						

Note : ** Symptoms (dyspnea/hemoptysis/caugh) no symptom = 0 , mild(normal activity daily life) = 1, moderate (some limitation of ADL) = 2

severe (total limitation of ADL) = 3 , Very severe (symptomatic at rest need admission) = 4

*** When have high risk for side effect

DOTS-Plus Health facility (Form 4.4)

ชื่อ-สกุลผู้ป่วย ..... **Project ID.No**.....**. TB. No**..... **MDR-TB no** .....

ประเภทกลุ่มตัวอย่าง กลุ่ม ศึกษา กลุ่มควบคุม ชื่อ ร.พ.....

Summarize of treatment follow-up

Symptom show	Day 0 (Base line)	Duration of treatment				
		Month 9	Month 12	Month 15	Month 18	End of treatment
Body wt						
Temparature						
RR						
Dyspnea sign						
Symptom**						
Direct smear						
TB culture						
DST						
CXR						
ADR ระบุ						
Lab ***						

Note : ** Symptoms (dyspnea/hemoptysis/caugh) no symptom = 0 , mild(normal activity daily life) = 1, moderate (some limitation of ADL) = 2

severe (total limitation of ADL) = 3 , Very severe (symptomatic at rest need admission) = 4

*** When have high risk for side effect

DOTS-Plus Health facility (Form 4.5)

Patient name ....ProjectID.No..... .TB.No..... MDR-TB no .....

Define sample case control Hospital name.....

Drug given for TB-HIV case Name data recorder.....

D/M/Y	ARV regimen	regimen for OI	regimen for OI	other drug for DM	other drug for HT	comment
May-52						
Jun-52						
Jul-52						
Aug-52						
Sept52						
Oct-52						
Nov-52						
Dec-52						
Jan-53						
Feb-53						
Mar-53						
Apr-53						
May-53						
Jun-53						
Jul-53						
Aug-53						
Sept53						
Oct-53						
Nov-53						
Dec-53						
Jan-54						
Feb-54						
Mar-54						
Apr-54						
May-54						
Jun-54						

DOTS-Plus Health facility (Form 4.6)

Patient name ..... **..Project ID.No**..... **.TB.No**..... **MDR-TB no** .....

Define sample case control **Hospital name**.....

การรับยา **ARV** โดยดูตร..... ชื่อยันทีกรับยา.....

M/Y	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Wt	AFB	X-ray
May-52																																		
Jun-52																																		
Jul-52																																		
Aug-52																																		
Sept52																																		
Oct-52																																		
Nov-52																																		
Dec-52																																		
Jan-53																																		
Feb-53																																		
Mar-53																																		
Apr-53																																		
May-53																																		
Jun-53																																		
Jul-53																																		
Aug-53																																		
Sept53																																		
Oct-53																																		
Nov-53																																		
Dec-53																																		
Jan-54																																		
Feb-54																																		
Mar-54																																		
Apr-54																																		
May-54																																		
Jun-54																																		

Note : Method to record : O=Directly observed , N = not supervised , x = ไม่ได้รับยา

DOTS-Plus Health facility (Form 4.7)

Patient name ..... **..Project ID.No**..... **.TB.No**..... **MDR-TB no** .....

Define sample **case** **control** **Hospital name**.....

OI Drug regimen .....

M/Y		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	other symptom
May-52																																
Jun-52																																
Jul-52																																
Aug-52																																
Sep52																																
Oct-52																																
Nov-52																																
Dec-52																																
Jan-53																																
Feb-53																																
Mar-53																																
Apr-53																																
May-53																																
Jun-53																																
Jul-53																																
Aug-53																																
Sep53																																
Oct-53																																
Nov-53																																
Dec-53																																
Jan-54																																
Feb-54																																
Mar-54																																
Apr-54																																
May-54																																
Jun-54																																

Note : **Method to record; O=Directly observed , N = not supervised , x = not given drug**

DOTS-Plus Program (Form 5(1))

ชื่อ สกุลผู้ป่วย ..... **Project ID.No... ..... .TB.No..... ... MDR-TB no ....**

ประเภทกลุ่มตัวอย่าง กลุ่มศึกษา กลุ่มควบคุม ชื่อ รพ.....

ขนาดของยาที่ใช้กษา ในแต่ละเดือน ตามสูตรยา.....

วันที่ของเดือน	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	หากขาดนี้ ระบุ
เม.ย.51																																
พ.ค.51																																
มิ.ย.51																																
ก.ค.51																																
ส.ค.51																																
ก.ย.51																																
ต.ค.51																																
พ.ย.51																																
ธ.ค.51																																
ม.ค.52																																
ก.พ.52																																
มี.ค.52																																
เม.ย.52																																
พ.ค.52																																
มิ.ย.52																																
ก.ค.52																																
ส.ค.52																																
ก.ย.52																																
ต.ค.52																																
พ.ย.52																																
ธ.ค.52																																
ม.ค.53																																
ก.พ.53																																
มี.ค.53																																
เม.ย.53																																
พ.ค.53																																

หมายเหตุ : ระบุลงในช่องของแต่ละวันที่รับยา **O=Directly observed , N = not supervised , x** = ไม่ได้รับยา

ลงชื่อ ผู้กรอกข้อมูล.....

DOTS-Plus Program (Form 06)

ชื่อ-สกุลผู้ป่วย .... Project ID No.............................. TB No................ MDR-TB no ....

ประเภทกลุ่มตัวอย่าง กลุ่มศึกษา กลุ่มควบคุม ชื่อ รพ......................................

ผลการตรวจทางด้านชันสูตร

วดป	CBC													urin																		
	Hb	Hct	WBC	G6PD	ESR	Neutrophil	Eosinophil	Basophil	lymphocytes	Monocytes	อื่นๆ			Specific gravity	pH	Leucocytess	nitrite	protein	glucose	ketones	Urobilnogen	bilirubin	bl-electhrocyte	bl-Hg	Cast	Epith cell	RBC	WBC	อื่นๆ			
เมย51																																
พค.51																																
มิย51																																
กค.51																																
สค.51																																
กย.51																																
ตค.51																																
พย51																																
ธค.51																																
มค.52																																
กพ.52																																
มีค.52																																
เมย52																																
พค.52																																
มิย52																																
กค.52																																
สค.52																																
กย.52																																
ตค.52																																
พย52																																
ธค.52																																
มค.53																																
กพ.53																																
มีค.53																																
เมย53																																
พค.53																																

ผู้รายงาน../ตำแหน่ง..

DOTS-Plus Health facility (Form 06.1)

Month	Result (AFB)			
	d/m/y	Sample No	Result	
			Direct	Consent
0				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
21				

Month	Result (Culture)				
	d/m/y	Sample No	Result from Media		
			Solid	Liquid	other
0					
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					

Month	Result from Identification			
	d/m/y	Sample No	Result	
			M.TB	N.TM

Month	Result HIV			
	d/m/y	Sample No	Result	

Month	Result Diabetis			
	d/m/y	Sample No	Result	

Name patient

TB. No..... MDR-TB.No.....

Sample defind

case

control

Hospital name.....

Name data recorder .....

Drug susceptibility testing (DST) results

Lab no.	d/m/y	S		H		R		E		Z		Km		Eq		Pto/Eto		PAS		Other			
		Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect

หมายเหตุ : Method for DST : R= resistance , S= Susceptible , C = Contaminate * Direct รายงานภายใน 1 เดือน และ Conferm indirect

DOTS-Plus Health facility (Form 06.2)

Patient name ..... **..Project ID.No**..... **.TB.No**..... **MDR-TB no** .....

Define sample **case** **control** **Hospital name**.....

Result of Laboratory exam

D/M/Y	LFT											other	other												comment
	Alkphos	SGOT	SGPT	Total Bilirubin	Direct Bilirubin	Total prot	albumin	globulin	uric acid	BUN	Cr	RBS	CD4												
May-52																									
Jun-52																									
Jul-52																									
Aug-52																									
Sept52																									
Oct-52																									
Nov-52																									
Dec-52																									
Jan-53																									
Feb-53																									
Mar-53																									
Apr-53																									
May-53																									
Jun-53																									
Jul-53																									
Aug-53																									
Sept53																									
Oct-53																									
Nov-53																									
Dec-53																									
Jan-54																									
Feb-54																									
Mar-54																									
Apr-54																									
May-54																									
Jun-54																									

Name data recorder...../position.....

DOTS-Plus with Mobile communication For Call Center (Form 07)

Patient Name ……………………………………… ID.Project No………… ……TB.No…………… MDR-TB No…………… ชื่อ รพ………………………

D/M	Time	Time of calling	Obstacles and strategies to solve the problem	D/M	Time	Time of calling	Obstacles and strategies to solve the problem
1	Day			17	Day		
	Noon				Noon		
	nigth				nigth		
2	Day			18	Day		
	Noon				Noon		
	nigth				nigth		
3	Day			19	Day		
	Noon				Noon		
	nigth				nigth		
4	Day			20	Day		
	Noon				Noon		
	nigth				nigth		
5	Day			21	Day		
	Noon				Noon		
	nigth				nigth		
6	Day			22	Day		
	Noon				Noon		
	nigth				nigth		
7	Day			23	Day		
	Noon				Noon		
	nigth				nigth		
8	Day			24	Day		
	Noon				Noon		
	nigth				nigth		
9	Day			25	Day		
	Noon				Noon		
	nigth				nigth		
10	Day			26	Day		
	Noon				Noon		
	nigth				nigth		
11	Day			27	Day		
	Noon				Noon		
	nigth				nigth		
12	Day			28	Day		
	Noon				Noon		
	nigth				nigth		
13	Day			29	Day		
	Noon				Noon		
	nigth				nigth		
14	Day			30	Day		
	Noon				Noon		
	nigth				nigth		
15	Day			31	Day		
	Noon				Noon		
	nigth				nigth		
16	Day						
	Noon						
	nigth						

DOTS-Plus Program (Form 8)

Form for sending sputum sample for Identify and DST (Drug susceptibility testing) of M.Tuberculosis TB center; DPC10

(Lab Serial No)	d/m/y	Name-surname	sex	age	Requirment		Hospital name of sample	Name of sender	Name of reciver
					Dx	follow-up			

ผู้รายงานข้อมูล.....

DOTS-Plus Program (Form 9)

Report Form for Identify and DST (Drug susceptibility testing) of M.Tuberculosis,TB center;DPC10

(Lab Serial No)	d/m/y	Name-Surname	sex	age	Identify result		DST result											
					M.TB	Non TB	S	H	R	E	Z	Km	Am	Cm	Fo	PAS	Cs	Pto/Eto

Note : R = resistance S = Susceptible C = Contaminated

Name of data recorder.....

DOTS-Plus Program (Form 10)

ชื่อ-สกุลผู้ป่วย .....**Project ID.No**.....**TB. No**.....**MDR-TB no** .....

ประเภทกลุ่มตัวอย่าง กลุ่มศึกษา กลุ่มควบคุม ชื่อ ร พ.....

สรุปผลการติดตามการรักษา

อาการ/ อาการแสดง	Day 0 (Base line)	ระยะการติดตามผลการรักษา					
		เดือนที่ 1	เดือนที่ 2	เดือนที่ 3	เดือนที่ 4	เดือนที่ 5	เดือนที่ 6
Body wt							
Temparature							
RR							
Dyspnea sign							
Symptom**							
Direct smear							
TB culture							
DST							
CXR							
ADR ***							
Lab ***							

หมายเหตุ : ** Symptoms (dyspnea/hemoptysis/caugh) no symptom = 0 , mild(normal activity daily life) = 1, moderate (some limitation of ADL) = 2

severe (total limitation of ADL) = 3 , Very severe (symptomatic at rest need admission) = 4

*** พิจารณาตรวจในกรณีที่ผู้ป่วยมีปัจจัยเสี่ยงต่อการเกิดผลข้างเคียงจากยา เช่น มีโรคตับ โรคไต หรือ มีสภาพที่บ่งชี้ว่าผู้ป่วยเสี่ยงจากข้างเคียงจากยาที่ใช้รักษา

Appendix C

Diagnosis of TB

Since TB is an infectious disease caused by Mycobacterium *(M)tuberculosis the* diagnosis of TB should (as far as possible) be by demonstration of *M.tuberculosis* on culture or acid-fast bacilli (AFB) on smear examination. The World Health Organization (WHO) has strongly recommended sputum smear examination as the preferred screening test and suggests examination of 3 deeply coughed out sputum samples – spot sample on day 1, overnight sample and a spot sample in the morning on day 2. Recently it has been shown that sputum smear positivity is greater than 90% where greater than 5 ml of sputum is use for smear diagnosis of pulmonary TB. Culture of M. tuberculosis is the gold standard for diagnosis of TB. Culture of mycobacteria is a much more sensitive test than smear examination and has been estimated to detect 10-100 viable mycobacteria per ml of sample and in case of active disease they are found to be 81% sensitive and 98.5% specific. Culture methods are also required for further drug sensitivity testing in cases of suspected drug resistant cases. Isoniazid and rifampicin resistance can be reliably measured; resistance to pyrazinamide, ethambutol, and streptomycin is more difficult due to limitations of technique. The therapeutic index for a given drug is low for certain second line drugs such as ethionamide, cycloserine, viomycin and para amino salicylic acid (PAS) and it leads to misinterpretation of results due to failure to distinguish between sensitive and resistant strains. Misdiagnosis of MDR-TB due to laboratory related errors has been reported recently.

Smear examination:

An important component of TB management is good quality smear microscopy to identify *M. tuberculosis* as acid-fast bacilli (AFB). As smear gives a quantitative estimation of bacilli being excreted, it is of vital clinical and epidemiologic importance in assessing the patient's infectiousness and to follow the progress of TB patients on chemotherapy.

The World Health Organization (WHO) has strongly recommended sputum smear examination as the preferred screening test and suggests w\examination of 3 deeply coughed out sputum samples as follows:

Day 1 – spot sample

Day 2- Overnight sample and a spot sample in the morning.

More than 3 bacilli on the whole smear are needed to consider the smear positive. Though AFB smear examination is an extremely simple test carried out in most laboratories, it requires dedicated effort to obtain accurate results. Hence, every effort should be made to establish reliable laboratories with adequate quality control.

Smear examination has the advantage of simplicity, availability and rapidity, but the sensitivity is affected by the skill and experience of the microscopist, the number of specimens examined and the concentration of organisms (5,000-10,000 per ml) in the sputum. The sensitivity of the most common procedures widely used i.e. Zeil-Nelson's (ZN) technique or

Fluorescent Microscopy (FM)

For AFB smear range from 22% to 78%. Smear positivity depends Upon proper collection of the sample; appropriate staining techniques, and the number of bacilli in the sample. Recently, sputum smear positivity has been reported in upto>90% cases where greater than 5 ml of sputum was used for smear diagnosis of pulmonary TB.

Smear examination of sputum and other body fluids/ itssues by Zeil-Nelson's (ZN) techmique or Fluorescent Microscopy (FM) is a rapid method of identifying AFB. A small proportion of patients with pulmonary TB may be smear negative, particularly children and the elderly. Also, probability of finding AFBs in extrapulmonary (paucibacillary) specimens is much lower. In such cases other options that can be used are a) smear and culture on sputum, gastric lavage or bronchial washings, body fluids e.g. pleural/ pericardial / ascetic fluid, cerebro spinal fluid (CSF) or tissue obtained from biopsy b) specific empiric anti-TB therapy (SEATT), or c) close monitoring until diagnostic tests confirm TB.

Culture:

Culture of *M. tuberculosis* is the gold standard for diagnosis of TB. Culture can be performed on sputum, gastric lavage, bronchial washings or broncho-alveolar lavage, bronchial washings or broncho-alveolar lavage (BAL), extra pulmonary site aspirates and tissue biopsy collected in saline. Bronchoscopic washings can be contaminated easily by tap water used to clean containers and inadequately sterilized bronchoscopes.

Culture of my cobacteria is a much more sensitive test than smear examination and has been estimated to detect 10-100 viable mycobacteria per ml of sample and in case of active disease they are found to be 81% sensitive and 98.5% specific. Another advantage of culture is that it allown specific species identification and testing for recognition of drug susceptibility patterns. Media used for cultivation may either be solid media like Lowenstein Jensen's (L-J) media, Middlebrooks 7H10 or liquid media like Middlebrooks 7H11. Bactec 460 TB Radiometric system and Mycobacterium Growth Indicator Tube (MGIT) 960 are most commonly used rapid broth based detection system for isolation and identification of *M. tuberculosis* complex in liquid media. A combination of liquid and solid media is a standard procedure accepted worldwide.

Positive smears with negative cultures (smear positive, culture negative, S+C-) are reported to occur in 0.3% to 3% of specimens studied. A negative culture result with a specimen containing tubercle bacilli may occur in patients receiving chemotherapy particularly those containing rifampicin due to organisms which may have lost the ability of grow in culture media and are practically dead. In patients who are not on chemotherapy other causes of S+C- are false positive results, exposure of specimens to sunlight or heat, prolonged storage before inoculation, inadequate culture media and deficient incubation. Most cases of S+C- convert to negative smears with continuation of same treatment regimen.

Drug Susceptibility Testing (DST):

Culture methods are also required for further drug sensitivity in cases of suspected drug resistant cases. Diagnosis if MDR TB requires demonstration of resistance to at least isonizid (H) and rifampicin (R) ("HR resistance"); hence

specific attention should be focused on measurement of resistance to isoniazid and rifampicin using standardzed laboratory techniques, which specify inoculums size and are calibrated between laboratories.

Types of Drug Resistance:

Primary Resistance: Caused due to infection with organisms, which are resistant to one or more anti-TB drugs in patients who has never had any anti-TB therapy before.

Initial Resistance: Defined as infection with strains resistant to one or more anti-TB drugs in a new TB patient. This category includes patients with primary resistance and undisclosed acquired resistance i.e. those who either do not remember prior treatment of refuse to divulge the information of past treatment.

Acquired Resistance (secondary resistance): This type of drug resistance arises during the course of the treatment and is usually due to non-adherence of recommended therapy or faultly prescription.

Multi-Drug Resistance (MDR): Refers to resistance to two or more of anti-tuberculosis drugs. It can be initial as well as acquired. Generally MDR is taken as resistance to at least both isoniazid and rifampicin.

Drug Susceptibility Techniques in Tuberculosis

Three methods have been described by the WHO viz. absolute concentration, resistance ratio and proportion method

Absolute concentration method: Here growth is taken ad the end point. It is also referred to as the Minimal Inhibitory Concentration (MIC) method. The method requires care in the choice of appropriate inoculum since resistance on the part of the microorganisms is clinically significant only when at least 1% of the total bacterial population develops resistance at the critical concentration. Critical concentration can be defined as the lowest concentration at which the susceptible bacilli fail to grow in presence of the drug.

Resistance ratio method: It determines the resistance ratio between the MIC of the strain of patients and MIC of reference strain ($H_{37}RV$). This test also requires proper adjustment of inoculum size. Since reference strain is also included in this

test it is more accurate than the absolute concentration method as slight changes in the drug concentration are adjusted for.

Proportion method: The ratio of the number of colonies obtained on the drug-containing medium to the mumber of drug-free medium gives the proportion of resistant bacilli. Thus it is a qualitative as well as a quantitative method as it gives the proportion of resistant bacilli to sensitive ones. Bactec 460 TB uses the proportion method and since detection is by radiometric analysis results obtained are quicker.

However, variations in laboratory methods in evaluation of _*M. tuberculosis* and drug susceptibility can lead to diagnostic errors in a certain percentage of patients. Misdiagnosis of MDR-TB due to laboratory related errors has been reported recently. The possible explanation has been cross contamination, with *M. avium* complex, suspected mislabeling and discrepant susceptibility tests due to poorly standardized techniques in different laboratories. An important issue also is the reliability of the techniques currently used to measure drug resistance.

Although isoniazid and rifampicin resistance can be reliably measured, resistance to pyrazinamide, ethambutol, and streptomycin is more difficult due to limitations of technique. The therapeutic index for a given drug is low for certain second line drugs such as ethionamide, cycloserine, viomlycin and para amino salicylic acid (PAS) and it leads to misinterpretation of results due to failure to distinguish between sensitive and resistant strains.

Other Diagnostic techniques available for TB and their limitations:

Radiology: Tuberculosis is a great mimic and no radiological picture can be characteristic of the disease. Chest radiograph can be helpful in localizing abnormalities but to establish the diagnosis tuberculosis, further examination is necessary. Only bacteriology can provide the final proof . Radiological findings are relevant only to a certain extent and are therefore recorded as

- Normal
- Abnormal
- Cavitatorly or non-Cavitatory
- Stable, worsening or improving

High rate of over diagnosis by X-ray is high penalty for relatively small gain in patients

That might be missed by microscopy. Computed tomography (CT) scan findings in tuberculosis are equally non-specific. However, in cases of mediastinal lymphadenopathy, peripheral rim enhancement with relatively low attenuation centers can suggest a diagnosis of tuberculosis in the appropriate clinical setting.

Diagnostic Test based on immunology:

Tuberculin skin tests (TST)

TST e.g. Mantoux test (MT) can be used as diagnostic aid. A positive test indicates presence of infection but not active disease. Positive TST can, however be used to indetify individuals for isoniazid preventive therapy (IPT)/chemoprophylaxis. If the initial MT is negative the test should be repeated within 1-2 weeks. This two-step MT may eliminate some false negative reactions.

A negative skin test does not exclude TB, and positive skin test alone does not establish the diagnosis.

A positive test indicates presence of infection but not active disease.

Reasons:

False Negatives: About 20% of patients with active TB may have negative skin tests, and some populations have an even higher incidence of false-negative results.

For example, 50% false negative rates have been reported in patients with asvanced HIV infection.

False positives: results may occur in patients infected by non tuberculous mycobacteria (NTM) e.g. *M. avium* complex

BCG vaccination: In countries where BCG vaccination has been widely used, the skin test is not useful, because individuals vaccinated with BCG will have a positive skin test.

It is useful to detect and treat new TB cases in countries where the incidence of tuberculosis is low, and the health care system works well.

Routine Blood investigations

Blood tests, which must be performed in a suspected case of TB, are estimation of haemoglobin (Hb) and white blood cell count (WBC). Low hemoglobin found in tuberculosis may be due to anemia of chronic infection and does not require routine iron/vitamin supplementation. WBC is particularly useful in HIV-TB co-infection, where total lymphocyte count of >2000 corresponds to CD4 count of 500 ("surrogate lymphocyte count"). Erythrocyte sedimentation rate (ESR) has no diagnostic or prognostic value. The patient should be screened for diabetes and counseled for HIV testing. Blood urea nitrogen (BUN)/serum creatinine help confirm normal renal functions. Liver function tests are not routinely recommended in all patients with TB but must be assessed in those with pre-existing liver disease.

Antimycobacterial Susceptibility Testing for Mycobacterium tuberculosis Complex Methods in this Study

1.1 Introduction

Current methods for susceptibility testing of M.tuberculosis complex (MTBC, i.e., M. tuberculosis, M.bovis, M africanum, M. microti, M. canettii) are based on proportion methods and are considered equivalent to the standard methods established by Canetti et al. The proportion methods used globally rely on a bacteriological definition of drug resistance that was developed in recognition of the difficulties in defining clinical resistance, "Resistance is defined as a decrease in sensitivity of sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild strains of human type that have never come into contact with the drug. For several decades the method of proportion using Middlebrook 7H10 agar has been considered the standard method in the United States and is described in this document.

The agar proportion and radiometric methods both define resistance as growth of greater than 1% of an inoculum of bacterial cells in the presence of a "critical" concentration of antituberculous drug. The critical concentrations of antituberculous drugs were adopted by international convention and represent the lowest concentrations of drugs that inhibit 95% of "wild strains' of M.tuberculosis that

have never been exposed to the drugs, while at the same time not inhibiting strains of M.tuberculosis that have been isolated from patients who are not responding to therapy, and that are considered resistant. The recommended critical concentrations of drug were originally determined in egg-based :Lowenstein-Jensen medium and equivalent concentrations of drugs were later established in Middlebrook 7H10 and 7H11 for the agar proportion method and in the media used in commercial susceptibility test systems. Every laboratory should test the susceptibility of MTBC to the critical concentration of drug for the test method they are using. The critical concentration is the standard that allow interpretation of tests by any of the procedures. When greater than 1% of the tested bacterial population in a clinical isolate becomes resistant to the critical concentration of a drug, that drug is not, or soon will not be, useful for continued antituberculous chemotherapy. In establishing critical concentrations for a new testing system, serial dilutions of drug may be tested to determine what drug concentration in the new test system gives the same result as the critical concentration using the reference agar proportion method.

Using the critical concentrations of primary antituberculous drugs (i.e., isoniazid, rifampin, ethambutol, and pyrazinamide), the results of in vitro susceptibility testing of these correlate well with clinical effectiveness in patients with tuberculosis. Data concerning testing of secondary antituberculous drugs (see Table 1), however, are mere limited. There is also little information on the correlation of in vitro susceptibility testing results and clinical outcome for most slowly growing, nontuberculous mycobacteria. Exceptions are testing Mycobacterium kansasii to rifampin (for which in vitro susceptibility test results based on the interpretive criteria used of MTBC have good correlation with clinical efficacy) and testing Mycobacterium avium to clarithromycin.

Although the agar proportion and rapid broth methods represent breakpoint susceptibility test using a single, critical concentration of drug, laboratories may test an additional higher concentration of isoniazid , however, can provide the physician with information about the level of drug resistance in deciding whether to continue therapy with isoniazid either at the usual dose or an increased dose.

User of this document should be aware that the standardized agar proportion method for susceptibility testing of MTBC described here is not a rapid test. To assure the earliest possible detection of resistant organisms, rapid methods are the recommended standard of practice for drug susceptibility testing of MTBC in the United States and many industrialized nations. Use of a broth susceptibility testing method, in conjunction with rapid methods for primary culture and identification, should provide MTBC susceptibility test results within an average of 28 days of specimen receipt. Laboratories should use this 28 day goal for reporting MTBC susceptibility test results to guide selection of the combination of primary culture, identification, and susceptibility test methods.

The recommended rapid broth methods for susceptibility testing of MTBC are commercial systems that have been cleared by the US food and Drug Administration (FDA). At the time this document was written, two such FDA-cleared systems were available. The manufacture has responsibility for determining appropriate drug concentrations and specific testing instructions. Therefore, the recommendations in this document do not include those testing instructions which are the manufacturer's responsibility. Rather, instructions are provided for the reference agar proportion method, using Middlebrook 7H10 agar. The agar proportion method is the standard against which new methods are evaluated. It is also used to confirm results obtained in commercial broth systems and to test additional drugs and/or concentrations of drugs that are not available in commercial test system. The first isolate of MTBC abtained from every patient should be tested. Susceptibility testing should be repeated if cultures fail to convert to negative after three months of therapy, or if there is clinical evidence of failure to respond to therapy. Any such rapid method utilized should have been previously demonstrated to produce results that correlate with those obtained with the standardized agar proportion method. If the results obtained for a patient's isolate tested against any agent, by any rapid method, indicate resistance, or if the results, by any rapid method, are in any way ambiguous of problematic, then repeat testing of the isolate against that agent using the standardized method of proportion may be warranted,

Simultanceoously, consideration should be given to testing the secondary agents, so that several drugs can be identified to which the isolate is susceptible.

The full panel of primary drugs for susceptibility testing of MTBC includes isoniazid (INH) at two concentrations (critical and higher concentration), rifampin (RIF), ethambutol, and pyrazinamide (PZA). This represents a combination of tests that provides the clinician with comprehensive information related to the four-drug therapy currently recommended for treatment of most patients in the United States with tuberculosis Including PZA and a higher concentration of INH in the primary panel provides immediate additional information about the efficacy of four-drug therapy when resistance is encountered. The full panel of primary drugs may also provide sufficient information to avoid unnecessary secondary drug testing when a strain of MTBC is resistant only to INH, which is the most frequent pattern in the United States. Drug susceptibility testing with rapid methods, however, is expensive, requiring that laboratories make decisions about a cost-effective panel. Laboratory directors should consult with their Pulmonary and/or Infectious Disease specialist and TB control officer when making decisions concerning reducing the number of drugs tested. The decision to test a reduced of expanded panel. (e.g., including streptomycin) of primary antituberculous drugs should be based on considerations of: 1) the patient population served; 2X prevalence of drug resistance;3) Standard drugs used for treatment within the community; and 4) the availability and timeliness of obtaining additional testing when resistance or drug intolerance is encountered. In many areas laboratiories may consider testing a reduced panel of primary drugs consisting of a single, critical concen tration of INH , RIF , and ethambutol. State, provincial and local public health laboratories serve as referral centers for mycobacterial testing, including drug susceptibility testing for MTBC. At a minimum, state and provincial public health laboratories should provide, or assure access to, the full panel of primary and secondary antituberculous drugs. This reference service is necessary to provide continued surveillance of drug resistance, and to rapidly augment testing for laboratories that may choose to test a reduced panel of primary drugs.

Whenever secondary drug testing is required, laboratories should avoid a 'piecemeal' approach to providing clinicians with additional drug susceptibility test results. This is a particular concern, because currently most secondary drug testing is performed using the slower agar proportion method. Whenever an isolate of MTBC is resistant to RIF or resistant to any two of the primary drugs, a comprehensive battery of susceptibility tests that includes all of the secondary drugs and additional (higher) test concentrations of the primary drugs should be performed. If such testing is not done in-house, the isolate should be immediately forwarded to a public health or other referral laboouatory

Case scenarios with recommendations for MTBC susceptibility testing are described in Appendix A

Agar Proportion Methood

The procedure is performed by inoculating equal quantities of several dilutions of a standardized inoculum onto agar-based medium with and withou5 the test drug. Separate, countable colonies should be observed on a control quadrant without any of the drug. The number of colony forming units (CFU) growing on the drug-containing medium compared with those growing on the drug-free medium are then determined and expressed as a percentage. Strains of tubercle bacilli in which growth on drug-containing media represents more than 1% of the number of colonies that develop on drug-free media are considered to be resistant to that agent. The agar proportion method using Middlebrook 7H10 agar medium (7H10 agar medium) is recommended by the U.S Public Health Service.

1.1 Antutiberculous Agents

Source

Antimicrobial standards or reference powders, for use with the agar proportion method, can be obtained from commercial sources. Most antimicrobial reference powders are also available from:U.S. Pharmacopoeial Convention, Inc.

Reference Standards Order Department 12601 Twinbrook Parkway, Rockville, MD 20852, USA

Pharmacy stock of other clinical preparations are not to be used. Acceptable drug standards bear a label the states the generic name, its assay

potency (usually expressed in micrograms(*g) pre mg of drug], and its expiration date. The antimicrobial powders are to be stored as recommended by the manufacturer or at -20°C or below in a desiccator (preferably in a vacuum). When the desiccator is removed from the freezer, it is to come to room temperature before it is opened (to avoid condensation of water).

1.2.2Weighing Antituberculous Drugs

All antimicrobial agents are assayed for inhibitory activity. These units may very widely form the actual weight of the drug, and they often differ between drug production lots. Thus, a laboratory must standardize its antimicrobial solutions based on assays of the lots of antimicrobial powders being used. Either of the following formulae may be used to determine the amount of drug or diluent needed for standard solution.

$$\text{Weight (mg)} = \frac{Volume(mL).Assay\ Potency(\mu g/mL)}{Assay\ \text{Potency}\,(\mu g/\text{mg})} \quad (1)$$

Or

$$\text{Volume (mL)} = \frac{Weight(mg).Assay\ Potency(\mu g/mg)}{\text{Concentration}\,(\mu g/\text{mL})} \quad (2)$$

The antimicrobial powder should be weighed on an analytical balance calibrated with National Institute of Standards and Technology (NIST; Gaithersburg, MD) weights (or other approved reference weights). If possible, more than 100 mg of powder should be weighed. It is advisable to accurately weigh a portion of the antimicrobial agent in excess of that reqired and to calculate the volume of diluent needed to obtain the final concentration desired as in formula 2 above.

Example: To prepare 100 ml of a stock solution containing 1,280 - g/mL of antimicrobial agent from an antimicrobial powder with a potency of 750 – g/mg (for example, streptomycin). It is necessary to accurately weigh 170 to 200 mg of the antimicrobial powder on an analytical balance. If the actual weight were 182.6 mg, the volume of diluent needed would then be:

$$\text{Volume (mL)} = \frac{(182.6mg)(Weight) \bullet .(750\mu g / mg)(Potency)}{(1280\ \mu g/\text{mL})(\text{Desired Concentration})} = 107.0mL$$

1.2.3 Selection and Concentration of Antutuberculous Drugs

The primary drugs are INH, RIF, ethambutol, and PZA. Table 1 lists the concentrations recommended for the first three drugs for use with the agar proportion method, using 7H10 or 7H11 agar medium. See Section 3.7 of this document for a discussion of susceptibility testing of PZA. Testing all of the secondary antituberculous drugs listed in Table 21 should be performed on all isolates of MTBC that are resistant to RIF or resistant to any two of the primary drugs.

1.2.4Preparation and Storage of Stock and Working Solutions.

Examples of stock solution concentrations of antituberculous drugs made from drug powders or lyophilized commercial products are noted in Table 2.

1.2.4.1Drug Powders

Stock solutions of antituberculous agents available as powders are to be prepared at concentrations of at least 1,000 • g/mL and preferably 10,000 μg/mL except as noted in **Table 2**, footnote . Approximately 100 mg of drug (depending on the potency) dissolved in 10 mL of sterile distilled water would yield a stock solution of 10,000 μg/mL

Some drugs must be dissolved in solvents other than water, In such cases it is necessary to only use sufficient solvent to solubilize the antimicrobial powder, and then dilute to the final stock concentration with sterile distilled water or appropriate buffer, as suggessted in Table 2.

Sterilize solutions using a membrane filter (e.g., cellulose nitrate or Mixed cellulose ester [nitrate and acetate] with a pore size of 0.22 μm. Paper, asbestos, or sintered glass filters, which may absorb appreciable amounts of certain antituberculous agents, are not to be used. The first 10 to 15% of the filtered solution is discarded, because initially, some of the drugs could adsorb to the filter.

Small volumes of the sterile stock solutions are dispensed into sterile polypropylene or polyethylene vials appropriate for low-temperature storage, carefully sealed, and stored for up to 12 months at – 70^{0}C . Thaw to room

temperature and use without delay, discard excess, and never refreeze. Lower concentration stock solutions and higher storage temperatures have also demonstrated satisfactory stability for 12 months (i.e.,capreomycin 1,000 μg/mL at -20^{0}C, streptomycin 2,000 μg/mL at 3 to 7^{0}C and PAS 2,000 μg/mL at 3 to 7^{0}C). In all cases, directions provided by the drug manufacturer are considered to be part of these general reconmmendations.

1.3 Preparation of Drug Medium

1.3.1 7H10 Agar Medium

7H10 agar medium is recommended for susceptibility testing. 7H11 agar medium, which can be of help in the recovery of INH-resistant strains of MTBC, is an acceptable alternative. Those who do use 7H11 agar should be aware that different concentrations of some antimycobacterial agent must be used with this medium (see Table 1). Inspissated egg media are not recommended.

7H10 agar medium is prepared from a dehydrated base as recommended by the manufacturer. After the agar is autoclaved, it is allowed to cool to 50 to 56 ^{0}C in a water bath before adding the required oleic acid-albumin-dextrose-catalase (OADC) supplement (warmed to room temperature, 22 to 25^{0}C) and the appropriate antimycobacterial agent. This medium is usually prepared in lots of 200 mL.

1.3.2 Agar Dilution Method

(1)Thaw a tube of the frozen stock of the drug and dilute with water to yield a working concentration (usually 200 to 10,000 μg/mL). To achieve the desired final concentration (see Table 2), add the appropriate volume of working solution to sterile 7H10 agar tempered in a water bath at 50 to 56^{0}C to reach a volume of 180 mL.

(2) Mix the agar thoroughly with OADC (20 mL for a 200 mL total volume) and the antituberculous drug solution.

(3) Dispense 5-mL amounts into labeled quadrants of a series of sterile plastic Petri plates, reserving one quadrant for 7H10 agar medium without any added drug.

(4) Dispense the media onto the plates as quickly as possible after mixing the component parts to prevent partial solidification of the agar in the mixing

container. The agar in each quadrant should be 3 to 4 mm deep. Allow the agar to solidify at room temperature.

(5) Before use or storange, plates should be thoroughly dried by placing the plates with lids partially removed, preferable in a laminar-flow hood for several hours or overnight.

(6) After drying, use the plates immediately, or store them in sealed plastic bags at 4 to 8^0C for no more than 28 days. Protect all plates from light during storage.

(7) Test several samples of each batch of plates for sterility by incubating at 35^0C for 48 hours; discard these samples.

1.4 indirect Susceptibility Test

For the Agar Proportion Method, susceptibility testing usually is performed using cultures already isolated in or on a growth medium. The preparation of a standard inoculum is critical, because variations in the number of bacilli in the inoculum can alter the interpretation of the test.

1.4.1Preparation of the Inoculum

1.4.1.1Inoculum from Solid Media for the Agar Proportion Method

The following steps should be followed:

(1)Tht inoculum may be prepared by scraping freshly grown colonies (not more than four g0 five weeks old) form the surface of the medium, taking care to sample all parts of the growth. Care should also be taken not to scrape off any medium. Primary cultures, rather than subcultures, should be used whenever possible.

(2)Broth subcultures may reduce the number of slowly growing resistant tubercle bacilli in the culture thus giving a 'false-susceptible' result.

(3)The bacterial mass is transferred to a sterile 16-x 125 –mm screw-cap tube containing 6 to 10 glass or plastic beads and 3 to 5 mL of Tween-albumin liquid medium, such as Middlegrook 7H9.

(4)The growth is first emulsified along the inside wall of the tube with the help of a spatula or applicator stick. After closing the cap, the contents of the tube are homogenized by vigorous agitation on a vortex mixer for one two minutes, using

precautions to obtain only swirling, centrifugal mixing rather than churning, which may result in increased aerosol production.

(5)The tube is allowed to stand for 30 minutes or longer to allow larger particles to dettle and to decrease the possibility of aerosol dispersion.

(6)The supernate suspension is withdrawn and transferred to another sterile glass tube, and the absorbance is adjusted by adding broth until the density is equivalent to that of a McFarland 1 standard. McFarland standards may be purchased commercially or prepared in-house using barium chloride and sulfuric acid.

(7)Freshly grown cultures in broth, usually 7H9. may be used for the inoculum. After mixing well, allow the suspension to settle for 30 minutes to reduce the aerosol at the top of the tube and allow large clumps to settle. Then adjust the turbidity of the superntant to the McFarland No. 1 standard.

1.4.2 Inoculation and Incubation of Media

1.4.2.17H10 Agar Plates

To inoculate the plates, perform the following steps:

(1) Prepare 10^{-2} and 10^{-4} dilutions of the standardized suspension in Tween-albumin broth, such as 7H9, or sterile saline or sterile water.

(2) Using s sterile, cotton-plugged pipet, inoculate 0.1 mL of the 10^{-2} dilution onto the control quadrant and onto each of the drug-containing quadrants (this can be done by inoculating three drops at different points on each quadrant of the agar plate).

(3) Similarly, inoculate 0.1 mL of the 10^{-4} dulution onto the control quadrant and onto each of the drug-containing quadrants in a second series of drug-containing plates.

(4) If the culture to be tested is old or scant growth is present, it may be necessary to use lower dilutions of the inoculum, such as 1:10 and 1:1000 , or to subculture the organism first in growth. For broth subculture, a portion of the culture on solid media is inoculated into 7H9 broth and the broth is incubated at 37 $\pm$ 1 ^{0}C, with daily shaking, until the turbidity matches that of a No.1 McFarland standard.

(5)Allow the inoculated plates to stand at room temperature until the inoculum spots are absorbed into the agar (i.e.,until the spots are dry).

(6) Seal the plates in individual CO_2 – permeable polyethylene bags.

(7) Incubate the plates medium-side down, at 37 $\pm$ 1 ^{0}C in an atmosphere of 5 to 10% CO_2 – Incubation under such an increased CO_2 atmosphere does not have a detrimental effect on the antimycobacterial drugs tested routinely in 7H10 agar medium. Colonies may be larger under CO_2 incubation conditions.

(8) The plates should be protected from light during incubation.

(9) Examine the plates carefully, preferably microscopically using a dissecting microscope, each week for a period of no longer than three weeks. If the colonies on the control medium are mature, resistance may be reported before three weeks. However, the interpretation “drug susceptible” should not be made until the third week.

Alternately, a modified indirect susceptibility method that requires less media can be considered. Organism dilutions of 10^{-2} and 10^{-4} are prepared as described above. One control quadrant without drug and all drug-containing quadrants are each inoculated with 0.1 mL of the 10^{-2} dilution. A second drug-free control is inoculated with 0.1 mL of the 10^{-4} dulution, which generally gives countable colonies (see Example 3 in Section 3.4.3.1)

1.4.3 Interpretation

The pathobillogy of MTBC differs from that of many other bacteria. MTBC is an intracellular pathogen, and in this regard it is important to be aware that the intracellular drug concentration and activity may differ considerable from the corresponding values in serum and/or other extracellular fluids. Also the infecting bacilli often are composed of differing mixtures of populations of actively growing, slowly growing, and latent organisms at different sites and inside walled-off tubercles; drug effectiveness may vary among these different populations. As a consequence of these aspects of MTBC infection, susceptibility testing of MTBC differ from the susceptibility testing of aerobic and facultative bacteria in the following ways that directly or indirectly impact the reporting of results:

Testing with any antimycobacterial agent is performed at two different concentrations at most.

There is not uniform consensus regarding the clinical relevance of the results of testing at a higher concentration when two concentrations are used; this is particularly true for INH

"Critical" concentrations of certain drugs (the concentrations thought to be most relevant for predicting clinical responsiveness) were established many years ago, and for some drugs the values for these concentrations differ depending on the testing medium used.

The reference agar proportion method employs a percentage calculation to determine resistance or susceptibility.

The reference BACTEC method for PZA susceptibility testing employs a calculation procedure unique to that determine resistance or susceptibility

Many user of susceptibility reports may be confused or even misled if only the results of growth at the tested concentration(S) or an MIC is reported without some interpretive comment. Therefore, at a minimum, for every drug tested, reports should include the nsme of the drug tested, as well ad a clinically helpful interpretive comment, such as "susceptible," "resistant," or "borderline," the last for PZA only. If a laboratory wishes to report the concentration at which drugs have been tested, it should also specify the testing medium and/or testing method used, and /or specify the equivalent reference method concentrations. (If the reference method equivalent concentrations are given, then stating the actual concentrations tested and/or the testing method is optional.) Laboratories using the reference agar proportion method also have the option of reporting percent resistance, if they so choose. However, at this time there is no evidence to suggest that a lower percent resistance may provide partial drug efficacy in the clinical management of the patient. To avoid confusion, whenever testing is performed at concentrations in addition of the "critical" concentrations (or their equivalents in methods other than the reference agar proportion method), the reference method equivalent concentrations should be specified. In the case of an organism tested against two concentrations of INH, to

the lower concentration of which the organism is resistant and to the higher of which it is susceptible, the following comment should be appended to the results: “These test results indicate low-level resistance to INH. Some evidence indicates that patients infected with strains exhibiting this level of INH resistance may benefit from contimuing therapy with INH. A specialist in the treatment of tuberculosis should be consulted concerning the appropriate therapeutic regimen and dosages.”

Some scenarios and sample reports are:

Sample 1. A laboratory testing INH only at the low (“critical”) concentration, using the reference agar proportion method, and the isolate in question shows no growth on the drug-containing quadrant and adequate growth on the drug-free quadrant:

Option A:

Antimycobacterial Agent	Interpretation
Isoniazid	Susceptible

Option B:

Antimycobacterial Agent	Concentration	Method	% Resistance	Interpretion
Isoniazid	0.2	Agar proportion	0	Susceptible

Sample 1. A laboratory testing INH only at the low concentration, using a rapid broth method and the isolate is determined to be susceptible at that concentration:

Option A:

Antimycobacterial Agent	Interpretation
Isoniazid	Susceptible

Option B:

Antimycobacterial Agent	Equivalent Reference Method Concentration (μg/mL)	Interpretation
Isoniazid	0.2	Suseptible

Option C::

Antimycobacterial Agent	Concentration	Method	% Resistance	Interpretion
Isoniazid	0.1	Bactec	0.2	Susceptible

Sample 3. A laboratory testing INH at both concentrations, using the reference agar proportion method, and the isolate in question shows 30 colonies on the drug – containing quadrant at the lower concentration, on colonies at the higher concentration, and 150 colonies on the drug-free quadrant:

Option A:

Antimycobacterial Agent	Concentration	Method	Interpretion
Isoniazid	0.2	Agar proportion	Resistant
Isoniazid	1.0	Agar Proportion	Susceptible (see note)

Option B:

Antimycobacterial Agent	Concentration	Method	% Resistance	Interpretion
Isoniazid	0	Agar proportion	20	Resistant
Isoniazid	2	Agar proportion	0	Susceptible (see note)

NOTE : These test results indicate low-level resistance to INH. Some evidence indicates that patients infected with strains exhibiting this level of INH resistance may benefit from continuing therapy with INH. A specialist in the treatment of

tuberculosis should be consulted concerning the appropriate theraqeutic regimen and dosages.

Sample 4 A laboratory testing INH at both concentrations, using a rapid broth method and the isolate in question, is determined to be resistant at the lower concentration but susceptible at the higher concentration:

Option A:

Antimycobacterial Agent	Equivalent Reference Method Concentration (μg/mL)	Interpretation
Isoniazid	0.2	Resistant
Isoniazid	1.0	Susceptible (see Note)

Option B:

Antimycobacterial Agent	Concentration (μg/mL)	Method	% Resistance	Interpretion
Isoniazid	0.1	ESP II	0.2	Resistant
Isoniazid	0.4	ESP II	1.0	Susceptible (see note)

NOTE: These test results indicate low-level resistance to INH. Some evidence indicates that patients infected with strains exhibiting this level of INH resistance may benefit from continuing therapy with INH. A specialist in the treatment of tuberculosis should be consulted concerning the appropriate theraqeutic regimen and dosages

1.4.3.1Interpretation of Growth Observed on 7H10 Agar follows:

The amount of growth in each quadrant is recorded as follows:

* 500 colonies (confluent growth)4+
* 200-500 colonies (almost confluent growth)3+
* 100-200 colonies2+
* 50-100 colonies1+
* <50 colonies: record the actual number of colonies

At least one of the control quadrants of the two dilutions should have countable (i.e.,at least 50) colonies; otherwise, the results are not valid. If the plate with the countable colonies on the control is not the same as the dilution with any countable colonies for the drug-containing quadrants, one can use the number of countable colonies from the higher dilution plates, multiply this number by the dilution difference between the two plates, and use this as the denominator when calculating the percent resistance. An example is given later in this section

If the control quadrant has 3+ or 4+ growth and there is no growth in the drug-containing quadrant, the results can be reported as susceptible. In most cases, it will be possible to estimate the proportion of resistant colonies as greater of less than 1% of the control population. Most of the culture results will be obviously susceptible or resistant (see examples below) and only in rare instances should there be an Interpretation of the modified indirect susceptibility method follows guide lines for interpretation of the standard indirect method. See example 3 for a sample calculation and interpretation.

The presence of microcolonies may represent true resistance, partial resistance, or may be a result of drug degradation followed by an overgrowth of susceptible organisms. One study reported that most strains that have microcolonies with ethambutol in the agar proportion method have ethambutol-susceptible results with BACTEC 460 TB. The significance of microcolonies is unknown . Since the frequency of microcolonies may vary from one laboratory to another, each laboratory should determine how to best report results. One approach is to always note the presence of microcolonies with a statement that their significance is unknown. If a laboratory opts not to report microcolonies associated with a specific drug such as ethambutol, this decision should be based on its own experience with microcolonies (e.g.,reprocucibility on repeat testing) and consultation with its TB specialist.

The first week reading at seven days is for the purpose of detecting the growth of contaminating bacteria or fungi, and for the detection of any rapidly growing mycobacteria. In the direct-susceptibility test, the growth of even the slowly growing mycobacteia may be evident within two weeks of incubation. Susceptibility

test results should not be reported on readings made after this short incubation time with the exception of a strain that is obviously resistant to the drugs, since drug-resistant tubercle bacilli can grow more slowly than susceptible strains. The optimal time for interpreting growth on plates is three weeks after inoculation. If the culture in the drug-free control has not grown at the three-weeks. The resaults of the test at the six-week reading, however, can be reported only for the agents to which the isolate appears to be susceptible, and if adequate growth exists in the drug-free quadrant. The reasons for this are not completely understood, but it is probable that the late-growing colonies escape drug action and begin to grow when the drug level in the medium drops below the minimal inhibitory concentration.

The formula for determining percentage of resistance and some examples are:

$$\% \text{ Resistant} = \frac{number \text{ of colonies on drug - containing quadrant.}}{number \text{ of colonies on control quadrant}} = 100$$

Example 1 Sample Calculation and Interpretation

	Growth on:		
Antimycobacterial Agent/Concentration	10^{-2}	10^{-4}	% Resistant
Control	4+	100 colonies	-
Isiniazid (0.2 μg/mL)	2+	10 colonies	10
Rifampin (1.0 μg/mL)	0	0 colonies	0
Ethambutol (5.0 μg/mL)	0	0 colinies	0

$$\% \text{ Resistant} = \frac{number \text{ of colonies on drug - containing quadrant (10).}}{number \text{ of colonies on control quadrant (100)}} = 10\%$$

Interpretation based on calculation, above: susceptible to RIF and ethambutol; 10% resistance to INH.

Example 2 Sample Calculation and Interpretation

	Growth on:		
Antimycobacterial Agent/Concentration	10^{-2}	10^{-4}	% Resistant
Control	4+	500 colonies	-
Isiniazid (0.2 μg/mL)	100 colonies	0 colonies	2
Rifampin (1.0 μg/mL)	0	0 colonies	0
Ethambutol (5.0 μg/mL)	0	0 colinies	0

$$\% \text{ Resistant} = \frac{number \text{ of colonies on drug - containing quadrant}(100). \bullet 100}{\begin{array}{l} n\text{umber of colonies on control quadrant } (50) \text{ multiplied} \\ \text{by the dilution factor, which is the difference between} \\ 10^{-4} \text{ and } 10^{-2}(100) \end{array}} = 2\%$$

Interpretation based on calculation above: susceptible to ethambutol and RIF; 2% resistanct to INH.

Example 3 Sample Calculation and Interpretation of the Medified Indirect Proportion

Method.

	Growth on:		
Antimycobacterial Agent/Concentration	10^{-2}	10^{-4}	% Resistant
Control	4+	5 0 colonies	-
Isiniazid (0.2 μg/mL)	2+		> 1
Isiniazid (1.0 μg/mL)	0		0
Rifampin (1.0 μg/mL)	0		0
Ethambutol (5.0 μg/mL)	25 colonies		< 1

Interpretation:Resistant to INH (0.2 μg/mL) (because colony xounts [2+] are greater than the 10^{-4} control [50 colonies]); and susceptible to ethambutol (because colony counts [25 colonies] are less than the 10^{-4} control [50 colonies]) , INH (1.0 μg/mL), and RIF

1.5Direct Susceptibility Test

1.5.1Principle

The direct drug susceptibility test is a procedure based on inoculation of drug-containing media with processed (concentrated after digestion and decontamination) sputum specimens that are smear-positive for acid fast bacilli (AFB) to determine the proportion or percentage of resistant MTBC in the patient's bacterial population method or by a commercial method that has been approved and validated by FDA for direct susceptibility testing.

The advantages of the test are:

Results can be reported within three weeks (from the time of specimen receipt in the laboratory) for a majority of smear-positive specimens.

The proportion or resistant bacteria recovered better represents the patient's bacterial population. It is cost-efficient. The disadvantages of the direct test are:

The inability to accurately calibrate the inoculum, which may result in insufficient or excessive growth on drug-free control quadrants.

Possible growth of contaminants, making results uninterpretable

The results of the test are valid only if the isolate is MTBC or *M. kansassii* (RIF only)

The total rate of failure for the direct method can reach 10 to 15% or more, which results in frequent retesting by one of the indirect methods

1.5.2 Agar Plates

The direct susceptibility test is performed using 7H10 or 7H11 agar. The number of drug-containing plates to be inoculated will vary depending on whether only primary or both primary and secondary agents are to be tested.

1.5.3Inoculation and Incubation

After the digestion and decontamination steps, and confirmation that the specimen is AFB smear-positive, the sputum specimen is inoculated onto drug-free (control) and drug-containing quadrants of the agar plates. The inoculum used is based on the results of the AFB smear, performed using a fluorochrome stain, as shown in Table 4. Each quadrant is inoculated with 0.1 mL of inoculum, except for specimens containing less than 5 AFB /field, in which case the inoculum is increased to 0.2 mL. After inoculation the plates are treated as described in steps 5 to 8 in Section 3.4.2.

The Plates are examined microscopically, using a dissecting microscope, without removing the plates from the polyethylene bags, at one, two, three, and six weeks of incubation, The results observea at one and two weeks of incubation are recorded onto a laboratory worksheet, but are not to be reported. The purpose of this examination is to evaluate for growth of contaminants and to determine (at two weeks) if a sufficient nember of microcolonies are present on the drug-free medium. Contamination or insufficient growth is usually an indication that the direct test may fail. In such cases, an indirect test can be initiated using growth from the initially inoculated media.

1.5.4Reporting and Interpretation

Results are reported after three weeks of incubation, if the colonies on drug-free medium are mature as described in section 1.4.3

Some isolates may not grow, or do not grow sufficiently after three weeks of incubation. If this occurs the plates should be reincubated and examined at six weeks. “Susceptible” results can be reported at six weeks if no growth appears on the drug-containing segment but resistance should not be reported at six weeks. Such a test must not be reported and is considered invalid, since the growth after this prolonged period of incubabion may b e result of partial of the antimycobacterial agents.

Appendix D

Drug	Adverse effects
Isoniazid	Mide: Rash, urticaria, acne, arthralgias, shoulder-hand Syndrome, drowsiness, mood changes Severe : Hepatitis, hypersensitivity, peripheral neuritis, Optic neuritis, anemia, pellagra, SLE syndrome, rarely Seizures, psychosis, and coma due to over dosage. Drug interactions: increased blood levels of phenytoin, Psychotic episodes with disulfiram
Rifampicin	Mide : abdominal distress, red discoloration of body fluids. Contact lenses may be irreversibly stained Severe : Hepatitis hypersensitivity, anemia, Thrombocytopenia, Flu like syndrome, acute renal failure, exfoliative dermatitis in HIV positive cases Drug interactions :prednisolone, digitoxin, quinidine, ketoconazole, propranolol, sulfonylureas, oral contraceptivies, oral anticoagulants and anti retroviral drugs (most Pls and NNRTLs)
Ethambutol	Optic neuritis
Pyrazinamide	Mide ; abdominal distress, arthalgia Servere : Hepatitis, hyperuricemia (rarely gout), Hypersensitivity (rare) flushing of skin, photosensitivity.
Streptomycin, Amikacin ,Kanamycin,	Hearing loss, ataxia, hypersensitivity, nystagmus, Proteinuria, neuromuscular blockade
Cycloserine	Mood and cognitive deterioration, psychosis, tremors, Serzures
Para amino Salicylic acid	Abdominal distress, diarrhea, hypothyroidism
Ciprofloxacin, Ofloxacin	Abdominal distress, headache, anxiety, tremors, Insomnia, diarrhea, hepatitis, arthralgia

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