ECONOMIC EVALUATION OF CEFTAZIDIME AND MEROPENEM FOR THE TREATMENT OF SEVERE MELIOIDOSIS, NORTHEASTERN REGION IN THAILAND

Miss Viriya Hantrakun

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Health Economics and Health Care Management
Faculty of Economics
Chulalongkorn University
Academic Year 2010

การประเมินทางเศรษฐศาสตร์ของยาเซฟตาซิดิมและเมอโรพิเน็ม ในการรักษาโรคเมลิออยโดซีสชนิดรุนแรงทางภาคตะวันออกเฉียงเหนือ ประเทศไทย

นางสาว วิริยา ห่านตระกูล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาเศรษฐศาสตร์สาธารณสุขและการจัดการบริการสุขภาพ
คณะเศรษฐศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2553

Thesis Title	**ECONOMIC EVALUATION OF CEFTAZIDIME AND MEROPENEM FOR THE TREATMENT OF SEVERE MELIOIDOSIS, NORTHEASTERN REGION IN THAILAND**
By	**Miss Viriya Hantrakun**
Field of Study	**Health Economics and Health Care Management**
Thesis Advisor	**Associate Professor Pongsa Pornchaiwisekul, Ph.D.**
Thesis Co-advisor	**Associate Professor Jiruth Sriratanaban, M.D., Ph.D.**

Accepted by the Faculty of Economics, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

.....Dean of the Faculty of Economics
(Professor Teerana Bhongmakapat, Ph.D.)

THESIS COMMITTEE

..... Chairman
(Associate Professor Siripen Supakankunti, Ph.D.)

..... Thesis Advisor
(Associate Professor Pongsa Pornchaiwisekul, Ph.D.)

..... Thesis Co-advisor
(Associate Professor Jiruth Sriratanaban, M.D., Ph.D.)

..... External Examiner
(Chanvit Tharathep, M.D.)

วิริยา ห่านตระกูล: การประเมินทางเศรษฐศาสตร์ของยาเซฟตาซิดิมและเมอโรพิเน็มในการรักษาโรคเมลิออยโดซีสชนิดรุนแรงทางภาคตะวันออกเฉียงเหนือ ประเทศไทย (ECONOMIC EVALUATION OF CEFTAZIDIME AND MEROPENEM FOR THE TREATMENT OF SEVERE MELIOIDOSIS, NORTHEASTERN REGION IN THAILAND) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ดร. พงศา พรชัยวิเศษกุล , อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: รศ. นพ. จิรุตม์ ศรีรัตนบัลล์. 81 หน้า

การประเมินทางเศรษฐศาสตร์นี้มีเป้าหมายเพื่อวิเคราะห์อัตราส่วนต้นทุนประสิทธิผลของยาเมโรพิเน็มถ้ามีการใช้ทดแทนยาเซฟตาซิดิมที่เป็นการรักษามาตรฐานของโรคเมลิออยโดซีสชนิดรุนแรงจากมุมมองของโรงพยาบาลศูนย์ในประเทศไทย การวิเคราะห์ต้นทุนประสิทธิผลดำเนินการโดยสร้างแบบจำลอง (modelling-based cost-effectiveness analysis) **ซึ่งใช้**ตัวแปรต่างๆจากผลการวิจัยทางคลีนิกที่ได้ทำการศึกษาวิจัยที่โรงพยาบาลสรรพสิทธิประสงค์ การวิจัยนี้ใช้แบบจำลองการตัดสินใจ (decision tree)เป็นตัวแทนกระบวนการในการรักษาโรคเมลิออยโดซีส ต้นทุนที่ถูกรวมในการคำนวณนี้คือ ต้นทุนในการนอนโรงพยาบาลและต้นทุนของยาที่ใช้ในการรักษา ผลการวิจัยจะถูกนำเสนอเป็นค่าต้นทุนต่อจำนวนปีชีวิตที่รักษาไว้ได้ (incremental life year saved) ทั้งนี้ให้แน่ใจถึงความน่าเชื่อถือของผลการวิจัย จึงมีการการวิเคราะห์ความไวของผลลัพธ์ (sensitivity analysis)ประกอบกับการวิเคราะห์หลักเพื่อตรวจถึงผลของความไม่แน่นอนของค่าตัวแปรต่างๆที่มีต่อผลการวิจัย

ผลการวิเคราะห์เบื้องต้นจากการวิจัยนี้พบว่าถ้าใช้ยาเมอโรพีเน็มแทนเซฟตาซิดิมจะเกิดต้นทุนเพิ่มขึ้น 31,000 บาท ต่อจำนวนปีชีวิตที่รักษาไว้ได้ โดยยาเมอโรพีเน็มาสมารถเพิ่มจำนวนปีที่รักษาไว้ได้มากกว่ายาเซฟตาซิดิมเป็นจำนวน 0.34 ปี ผลจากการวิเคราะห์เมโรพิเน็มไม่แสดงความได้เปรียบทางต้นทุนประสิทธิผลอย่างสิ้นเชิง เนื่องจากยานี้ให้ประสิทธิผลเพิ่มขึ้นแต่ก็ยังผลให้มีต้นทุนเพิ่มขึ้นเช่นกัน โดยต้องใช้ต้นทุนที่เพิ่มขึ้น 90,338 บาท ต่อ 1 ปีที่เพิ่มขึ้นของชีวิตที่รักษาไว้ได้ และจากการการวิเคราะห์ความไวของผลลัพธ์แบบที่ละตัว (one way sensitivity analysis)พบว่าผลการวิเคราะห์นั้นแปรเปลี่ยนได้ง่ายเมื่อตัวแปรของโอกาสในการเสียชีวิตภายใน 48 ชั่วโมงและโอกาสในการเสียชีวิตหลังการรักษาล้มเหลวมีค่าที่เปลี่ยนแปลงไป และถึงแม้ว่าผลของค่าต้นทุนประสิทธิผลข้างต้นจะแสดงว่ายาเมอโรพิเน็มให้ความคุ้มค่าทางการแพทย์เพราะต้นทุนที่เพิ่มขึ้นมีค่าน้อยกว่าระดับความเต็มใจที่จะจ่าย 100,000 บาท (willingness to pay threshold) แต่จากการวิเคราะห์ความไวแบบอาศัยความน่าจะเป็น (Probabilistic sensitivity analysis) บ่งชี้ว่าการมีความเป็นไปได้สูงที่ข้อสรุปนี้อาจไม่ถูกต้อง ทั้งนี้เพราะมีความไม่แน่นอนในค่าตัวแปรหลายตัวในแบบจำลอง ฉะนั้นจึงยังไม่สามารถสรุปได้ว่าควรใช้ยาเมโรพิเน็มแทนการรักษามาตรฐานด้วยยาเซฟตาซิดิมจากผลการวิเคราะห์ต้นทุนประสิทธิผลในครั้งนี้ ขณะนี้มีการวิจัยทางคลีนิกที่เปรียบเทียบประสิทธิภาพระหว่างยาเซฟตาซิดิมและเมอโรพิเน็มอยู่ในขั้นดำเนินการเก็บข้อมูล และเมื่อใดที่มีการรายงานผลของการวิจัยทางคลีนิกนี้ การวิเคราะห์ทางเศรษฐศาสตร์จะถูกทำซ้ำเพื่อให้ได้ผลสรุปที่แน่นนอนและแม่นยำมากยิ่งขึ้น

สาขาวิชา เศรษฐศาสตร์สาธารณสุขและการจัดการบริการสุขภาพ ลายมือชื่อนิสิต.....Viriya Hanatrakul.....

ปีการศึกษา 2553 ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม.....

##5385733029 : MAJOR HEALTH ECONOMICS AND HEALTH CARE MANAGEMENT
KEYWORDS : COST-EFFECTIVENESS / ECONOMIC EVALUATION/ MELIOIDOSIS / MEROPENEM / CEFTAZIDIME

VIRIYA HANTRAKUN : ECONOMIC EVALUATION OF CEFTAZIDIME AND MEROPENEM FOR THE TREATMENT OF SEVERE MELIOIDOSIS, NORTHEASTERN REGION IN THAILAND ADVISOR : ASSOC. PROF. PONGSA PORNCHAIWISEKUL, Ph.D.,
CO-ADVISOR : ASSOC. PROF. JIRUTH SRIRATANABAN, M.D., Ph.D., 81 pp.

This economic evaluation aims to determine the incremental cost-effectiveness of Meropenem if used instead of Ceftazidime in treatment of severe Melioidosis from the perspective of regional hospitals in Thailand.

A modelling-based cost-effectiveness analysis was performed based on a published randomised controlled trial conducted in Sapprasitprasong Hospital. A decision tree was used to represent the course of melioidosis treatment. Two major costs incurred to the hospital were included in the analysis; hospitalization cost and drug cost. The result is expressed as cost per incremental life year saved. To ensure the reliability of study results, extensive sensitivity analyses were used to handle uncertainties in model parameters.

Results from this preliminary study suggest that the incremental cost for treatment with Meropenem instead of Ceftazidime is 31,000 Baht. Meropenem increases life years by 0.34 years compared to Ceftazidime. Meropenem is not a dominant choice of treatment because it provides higher effectiveness but with higher cost of treatment; the incremental cost effectiveness is 90,338 Baht per one additional life year saved. One way sensitivity analysis showed the result was highly sensitive to probability of death within 48 hours and death rates after treatment failure. Probabilistic sensitivity analysis suggested that although the baseline result suggests that Meropenem is more cost-effective as the ICER is lower than the WTP threshold of 100,000 Baht, there is a high probability that this conclusion might be wrong due to the uncertainty in many parameter estimates. Therefore, it is inconclusive that Meropenem should be adopted to replace the standard treatment from this analysis. There is an ongoing randomised controlled trial comparing the effectiveness of Ceftazidime and Meropenem; when the trial result is available this analysis will be repeated for more robust results.

Field of Study : Health Economics and Health Care Management
Academic Year : 2010

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

ACKNOWLEDGEMENTS

I am heartily thankful to my supervisor, Assoc. Prof. Pongsa pornchaiwisekul, and my co-advisor, Assoc. Prof. Jiruth sriratanaban, Assoc. Prof. Siripen Supakankunti, Dr. Chanvit Tharathep who had encouraged, supervised and supported from the preliminary to the completion of the thesis project which enabled me to develop an understanding of the subject.

I offer my gratitude to Dr. Direk Limmathurotsakul, Dr. Yupin Suputtamongkol who provided expertise opinions regarding melioidosis and Dr. Yoel Lubell who had provided guidance on economic evaluation and analysis tool.

Lastly, I would like to thank my classmates for creating an energetic environment of learning in classes and faculty staff; Khun Kingthong Gonganoi for her administrative facilitation in every step of this educational journey.

CONTENTS

Page

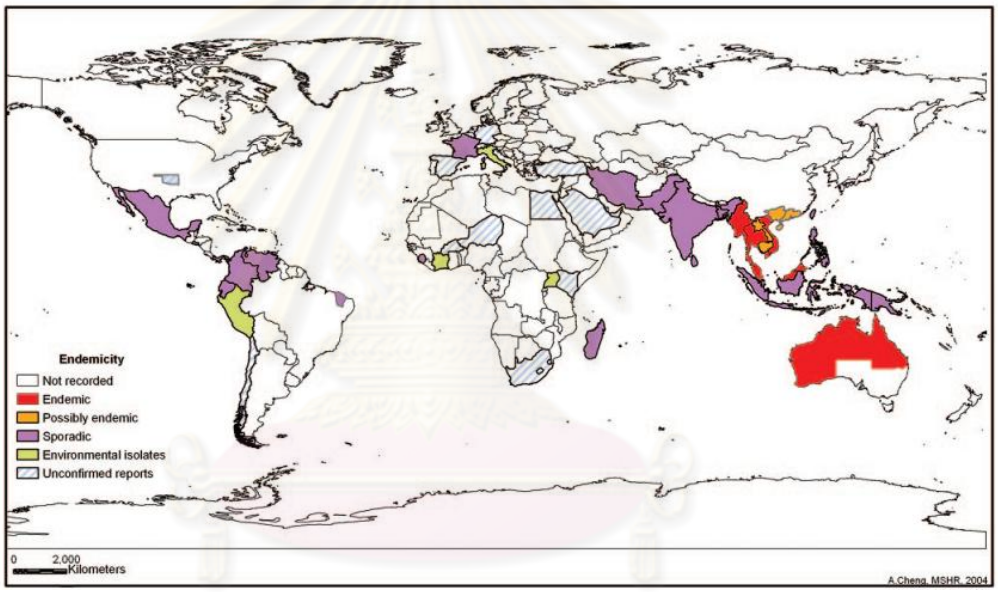
CHAPTER I
INTRODUCTION

1.1 Background

Melioidosis

Melioidosis is an infectious disease caused by bacteria *Burkholderia pseudomallei*. The endemic areas are Northern Australia, Indian subcontinent, South America, and Southeast Asia.(Figure 1.1)

Figure 1.1 Worldwide distribution of melioidosis



Source: Cheng and Currie, 2005

From the Annual Epidemiological Surveillance Report 2007 by the *Bureau of Epidemiology*, Department of Disease Control, Ministry of Public Health, the top 10 endemic provinces in Thailand were Ubon Ratchathani, Khon Khan, Srisaket, Mukdahan, Amnat Chareon, Roi Et, Nong Bua Ram Phu, Yasothon, Prachin Buri, Karasin. Most of the provinces are in the northeastern region.

Humans can be infected with *B. pseudomallei* through oral, nasal or skin exposure to soil and water in endemic locations. Most patients are farmers and the poor from rural areas. The incidence of the infection is very high during raining season when the farmers are most exposed to muddy environment. Melioidosis is considered a major

cause of community-acquired septicaemia in northeast Thailand (Chaowagul et al., 1989).

Underlying diseases

Common manifestations include cavitating pneumonia, hepatic and splenic abscesses, and soft tissue and joint infections. Melioidosis has a very high in-hospital mortality rate of up to 48%. Diabetes and renal impairment are common in the northeast Thailand and both are significantly associated with melioidosis (Chaowagul et al., 1993).

Burden of disease

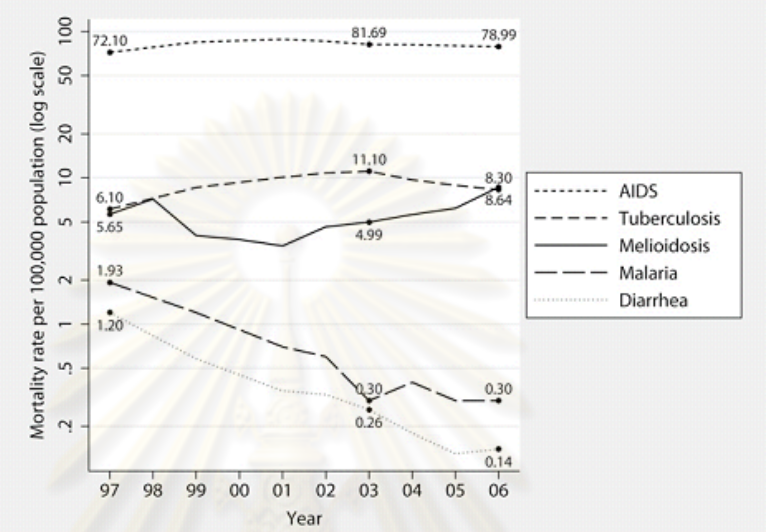
According to the latest report from Limmathurotsakul (2010), the mortality rate of severe melioidosis was 38% - 48% varied over 10 years records of Saprasitprasong Hospital from 1997 – 2006 (Table 1.1). Melioidosis incidence sharply increased from year 2000 to 2006; 8.0 to 21.3 cases of melioidosis per 100,000 population in Ubon Rachathani. The average mortality rate was 42.6% which made melioidosis the third most common cause of death from infectious diseases after HIV AIDS and tuberculosis in the Northeast. (Figure 1.2)

Table 1.1 Incidence of melioidosis and associated death rate between 1997 and 2006 in Ubon Rachathani

Year	Average annual rainfall (mm) in Ubon Rtachathani province	Melioidosis patients (N)	Deaths	Mortality rate	Incidence rate per 100,000 people	Mortality rate per 100,000 people
1997	1,555.1	198	97	49.0%	11.53	5.65
1998	1318.3	257	124	48.2	14.85	7.16
1999	1582.5	173	71	41.0	9.83	4.04
2000	1844.6	141	67	47.5	7.98	3.79
2001	1709.4	152	61	40.1	8.54	4.43
2002	1677.3	184	83	45.1	10.26	4.63
2003	1560.4	135	90	38.3	13.02	4.99
2004	1471.1	150	99	39.6	14.18	5.62
2005	1323.0	273	110	40.3	15.38	6.20
2006	1526.7	380	254	40.5	21.31	8.64

Source: Limmathurotsakul et al., 2010

Figure 1.2 Mortality rates from infectious diseases per 100,000 people in Ubon Ratchathani province between 1997 and 2006.



Source: Limmathurotsakul et al., 2010

Melioidosis is not only a life threatening disease, but also causes recurrent infections. Recurrence can occur due to relapse (caused from the first infection) or reinfection (new infection). Maharjan et al., 2005 reported that although patients had been treated with proper antimicrobial treatment, melioidosis is still associated with a high recurrence rate, with 75% relapsed and 25% experiencing reinfection. Recurrence time varies in each patient from months to years. The median time of relapse was 228 days and median time to reinfection was 823 days. The mortality rate of first relapse was 32% (Chaowagul et al., 1993).

Melioidosis treatment

The treatment of melioidosis consists of 2 phases; first is acute phase (first 2 weeks) where intravenous Ceftazidime, imipenem or Meropenem will be administered to patients. In the second phase commonly called eradication phase, a standard combination of 2 antibiotics will be prescribed (Doxycycline and Co-trimoxazole) for 20 weeks to prevent recurrent infections (Department of Medical Science, Ministry of Public Health, 2011: online).

Severely ill patients with suspected melioidosis infection are treated with Ceftazidime as a standard antimicrobial treatment. In Sapprasithiprasong hospital, Ceftazidime is used as the first line treatment since the clinical trial result showed that Ceftazidime halves mortality rate from 80% to 35% compared with the previous standard regimen (doxycycline + chloramphenicol + co-trimoxazole) (White, Dance, Chaowagul, Wattanagoon, Wuthiekanun, Pitakwatchara., 1989). However, rates of deaths occurring within 48 hours, where most of total deaths occur, have not been successfully reduced. This has led to the search of other antimicrobial drugs that can save more lives in the first 48 hours of hospitalization.

Meropenem is not currently the standard treatment for melioidosis and is a very expensive drug. Meropenem will be used to treat critically ill patients with bacterial infection or patients with antibiotic resistant infections. Laboratory tests have shown that the bacteria causing severe melioidosis (*B. pseudomallei*) can be killed within 6 hours (Smith, Wuthiekanun, Walsh, White., 1994). Therefore, Meropenem might be another choice of drug for severe melioidosis treatment.

Because of the severity of the disease, melioidosis patients are often hospitalized for weeks or even months. This makes melioidosis one of hardest infectious diseases to manage and demands high medical resource consumption. Since most of the patients are poor, cost of treatment has been subsidized by the universal coverage scheme implemented since 2002. Possible benefits from Meropenem are shorter hospitalization days, and medical resource consumption may be less. Meropenem may therefore be more cost-effective than Ceftazidime for severe melioidosis treatment.

1.2 Rationale

Melioidosis places a large burden to health care management in northeastern Thailand. The disease severity requires high health care resource consumption in both secondary and tertiary care hospitals. Simpson (1999) reported that the average cost of survivors ranged from 800 to 1450 US dollars; approximately 24,000 to 43,500

Baht (converted at 30 Baht per 1 dollar). With the inflation rate the treatment cost is expected to be much higher, approximately 50,000 Baht.

Severe melioidosis burdens not only the health care sector but also society in general. It is a health threat affecting particularly the low income population. Because most of the infected patients are agricultural working people who generate most of the income to their household, this inevitably has an impact on the household economy as a whole.

High mortality rate within 48 hours still challenges melioidosis management. Current standard treatment with Ceftazidime effectively reduces overall mortality rate but early death is still high. Meropenem is a new hope to overcoming this challenge. It is currently being investigated whether Meropenem is more effective and can reduce death rates as compared with Ceftazidime for severe melioidosis treatment in a clinical trial with a sample size of 705 in five sites in the northeast of Thailand. The principle investigator is Dr. Wirongrong Chierakul. The preliminary analysis is expected to be done in early 2012 and the final study result may be available in a few years.

Even if the trial shows Meropenem to be more effective, it will also need to be shown to be cost-effective before it can be recommended for use in routine practice. No economic evaluation has ever been carried out for the treatment of melioidosis. This analysis therefore focuses on the cost effectiveness of Ceftazidime that is already in routine use, and of Meropenem, which is being considered for adoption if found to be more effective. With the possibility of further clinical effectiveness data becoming available, this analysis is a preliminary one that will be conducted again once the new evidence is available.

1.3 Research Questions

Is Meropenem more cost effective than standard treatment, Ceftazidime, for the treatment of severe melioidosis?

1.4 Objectives

1.4.1 General objective

To determine the incremental cost-effectiveness of Meropenem if used instead of Ceftazidime in treatment of severe melioidosis from the perspective of regional hospitals.

1.4.2 Specific objectives

a) To conduct a decision analysis to estimate the effect of severe melioidosis treatment (Ceftazidime and Meropenem) on mortality rates based upon current best evidence in the published literatures
b) To estimate the costs associated with disease management incurred to health care providers from each treatment
c) To conduct extensive sensitivity analysis to explore the impact of uncertainty on the results

1.5 Scope of the Study

This study is a preliminary analysis of cost-effectiveness comparing Ceftazidime and meropemen for the treatment of severe melioidosis from the health care provider's perspective. Although the full course of melioidosis treatment is composed with 2 phases, parenteral antibiotics for acute infection phase then the combination of antibiotics for eradication phase. The analysis aims to study the acute severe of melioidosis management drugs which are Ceftazidime and Meopenem. The only course of treatment incur during hospitalization will be taken into account.

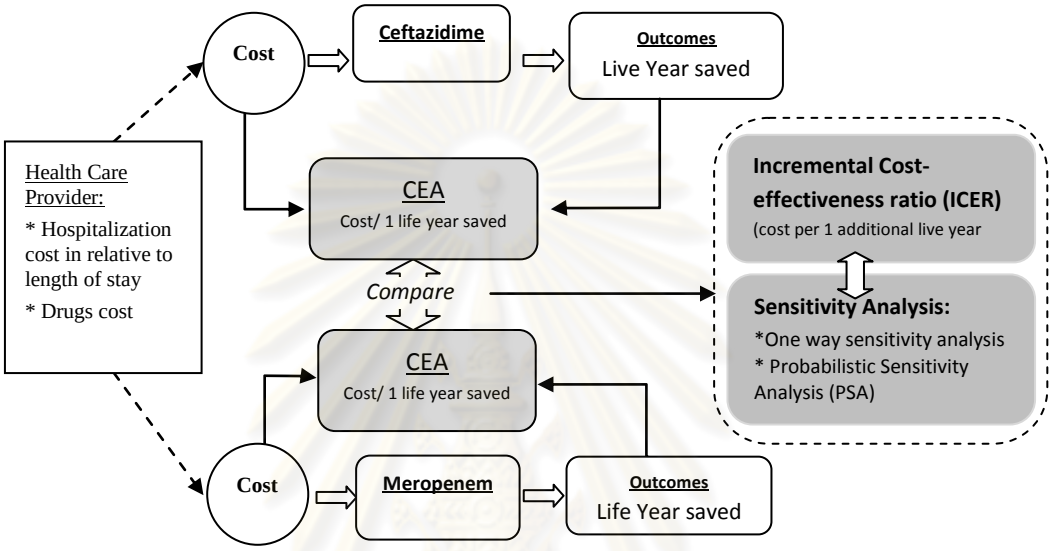
1.6 Conceptual Frame Work

This economic evaluation aims to compare the cost and outcomes of the two parenteral antibiotics for severe melioidosis and to explore the impact of the uncertainties surrounding the parameters. There are three main components to the conceptual framework. (Figure 1.3)

Firstly, the outcomes and cost of the each treatment will be indentified. For the purpose of preliminary analysis, only hospitalization and drug cost will be included.

Secondly, the ratio of cost per outcome of each treatment will be compared and presented as Incremental Cost-Effectiveness Ratio (ICER). Thirdly, sensitivity analyses will be conducted to test the robustness of study results.

Figure 1.3 Conceptual frameworks



1.7 Possible Benefits

Because no economic evaluation for severe melioidosis treatment has been done, the study result will be informative both for policy makers considering the cost-effectiveness of the specific treatments in this analysis, but also for economic evaluations of melioidosis treatments for other drugs and contexts.

1.8 Thesis structure

This chapter has described the burden of melioidosis and the research question in this thesis. Chapter 2 presents a literature review that was carried out to identify key information regarding the natural history, effectiveness and treatment outcomes that help in structuring the decision analytic model used in this analysis. The information from literature review then formed the research methodology presented in chapter 3. This is followed by the analysis results and discussion the last two chapters.

CHAPTER II
LITERATURE REVIEW

Two literature reviews were carried out to derive research design and to obtain parameter estimates for the decision model. The first type was a review of the medical literature searching for evidence concerning melioidosis patients' characteristics, its diagnosis, clinical course and treatment data. This information was used to structure the decision analytic model and also to identify the possible values of parameters required in the model. The second literature review was for economic evaluations of infectious diseases treated with the antibiotics under consideration in this analysis. The aim here was to find examples of types of models, model parameters, cost estimation, and sensitivity analysis techniques used in similar analyses.

The literature reviews initially located relevant studies in an online database using the following keywords for the medical literature review: melioidosis in combination with treatment and/ Meropenem, Ceftazidime. The second review for economic evaluations of infectious disease treatments used the following keywords: cost-effectiveness in combination with Meropenem and severe infection. The bibliographies in identified papers were searched for any additional relevant papers.

2.1 Medical Literatures

In model-based economic evaluations, it is critical to structure the model to be able to represent real clinical course and the management of the disease of interest as closely as possible. Therefore, clinical literatures will be reviewed to identify patient characteristics (to indicate possible health benefits i.e. life expectancy), diagnosis and clinical course (for details of possible clinical procedures, their costs and possible adverse events) and treatment of melioidosis (primarily for estimates of effectiveness parameters).

2.1.1 Patients Characteristics

Report from the Bureau of Epidemiology, Ministry of Public Health (2007) and Limmathurotsakul (2010) showed similar characteristics of melioidosis patients. Men were infected with the disease more than women (Female 1: Male 1.5). 50% of the

patients were farmers. The median age of patients was 49 years and the highest rate of infection was found amongst patients between the age of 45 and 65.

Table 2.1 Characteristics of melioidosis patients between 1997 and 2006 in Ubon Rachathani

Population	Cases in this study	Total population*	Annual incidence of melioidosis (per 100,000 people)
Total population	2,217	1,745,364	12.7
Sex			
Female	921	875,727	10.5
Male	1,296	869,638	14.9
Age (years)			
<15	199	418,459	4.8
15-24	71	315,076	2.3
25-34	193	341,134	5.7
35-44	402	272,645	14.7
45-54	528	181,646	29.1
55-64	503	110,835	45.4
65-74	248	68,691	36.1
>75	73	36,878	19.8
Diabetes			
No diabetes	1,123	1,656,090	6.8
Known diabetes	662	45,448	145.7
Undiagnosed diabetes	370	43,826	84.4

Source: Limmathurotsakul et al., 2010

The patients sought treatment mostly at community hospitals at 44%; others were treated at general hospitals (28%) and regional hospitals (24%). 42% were in-patients and 58% were out-patients (BOE, MOPH, 2007).

2.1.2 Diagnosis of Melioidosis

For every severely ill febrile patient who lives in endemic area should be suspected of melioidosis (White, 2003). Because sign and symptoms of melioidosis are similar to other bacterial infections therefore the diagnosis procedures done and antibiotic prescribed are highly rely on clinician's preferences and experiences with clinical prognosis of melioidosis. Specific diagnostic test such as x-ray and ultrasound are proscribed when clinical signs of lungs or abdominal shown at the admission. White (2003) suggested that abdominal ultrasound should be done in all suspected cases as a hepatic abscess is one of the main characteristic of melioidosis.

Serology test is commonly used in endemic areas (Cheng, 2010). Serology's specificity ranges from 37% to 64% and sensitivity ranges from 73% – 86% depending on methods used (IHA, IgM ICT, IgG ICT and ELISA) (Cheng et al., 2005). The gold standard of melioidosis infection is still a bacteria culture, however this can be a lengthy process. "a delay of 24 to 48 hours or more between time of specimen platting and bacterial growth plus presumptive identification often occurs" (Wuthiekanun et al., 2005). Specificity of culture is considered 100% because *B. psuedomeliei* are not normally found in healthy people. The sensitivity of culture was found to be low at 60.2% hence culture is an imperfect gold standard (expected sensitivity to be 100%). From this analysis the author suggested that in hospitals where high incidence of melioidosis, all suspected melioidosis patients should be treated with antibiotics that cover *B. pseudomeliei* and be discontinued or changed to other agents if a diagnosis is made excludes melioidosis (Limmathurotsakul et al, 2010).

2.1.3 Clinical course

- The response to treatment was slow. Median hospital stay was 20 days (8-74 days) (Chaowagul et al., 1988). Clinical characteristics of patients were septicemia (59.8%), renal failure (31%), septic shock and respiratory failure (18.4%). Type/ site of infection were septicemia (65.2%), Lung (50%), skin/ soft tissue infection (39%), intra-abdominal abscess (30.4%) and bone or join infection (15%) (Chierakul et al., 2005).
- Unpublished data from a prospective observational study of intra-abdominal abscess in melioidosis conducted by Maude et al.(2011) at Sapprasitprasong hospital shows that 46% (77/ 164) of melioidosis patients had either splenic or hepatic abscess and 30% (23 of 77) patients had both hepatic and splenic abscess. Mortality in this group was 10% and median length of stay was 9 days (range 4-15 days).
- Another major underlying disease highly associated with melioidosis infection is diabetes, because diabetes patient are more prone to bacterial sepsis than the general population. Goh et al. (2011) studied 1160 patients infected with sepsis caused from *Burkholderia pseudomallei*. This study aimed to compare the

survival after sepsis between diabetics and non-diabetics in melioidosis patients. The result indicated that the survival rate in the diabetics was higher than non-diabetics patients. This survival benefits occurred in the diabetics patients who were treated with anti-inflammatory in the glyburide group.

2.1.4 Relapse in Melioidosis

- Limmathurotsakul, Chaowagul, Day, and Peacock. (2009) studied specifically the recurrent characteristic of melioidosis. They reported that recurrent rate (Relapse and re-infection) was 12.7% for patients who survived severe melioidosis within the first year. Mortality of melioidosis relapse was 27% compared with 42% for the primary infection (Chaowagul et al., 1993). There are two causes of recurrent episodes; relapse and re-infection of *Burkholderia pseudomallei*. 65% of recurrent episodes were caused by relapse and the other 35% was from re-infection.
- A comparative study was conducted in 118 patients from 1986 to 1991 aiming to measure the occurrence of relapse in melioidosis patients by Chaowagul et al., (1993). There were 3 parenteral antibiotics used for acute phases (cetazidime, doxycycline, or a combination of chloramphenicol+doxycycline+cotrimoxazole) and oral drugs were prescribed according to physician preference and availability. A long-term follow up found culture-confirmed relapse in 23% of patients. The relapse rate per year was 15%. The median time from discharge to relapse was 21 weeks (range 1-290 weeks). 27% of patients with relapse died. Patients with more severe disease (septicaemia) had higher relapse rates of up to 4.7 episodes compared to patients with localized melioidosis. Underlying disease was not associated with relapses.

  The study also observed that Ceftazidime reduced the risk of relapse by 2-fold. This report however differs from the report made by Limmathurotsakul et al. (2006) that relapse in melioidosis were not associated with the choice of parenteral antibiotic (Ceftazidime, carbarpenem antibiotics and augmentin) and the duration of intraveneous therapy was also not related to the risk of relapse.

However, the two study similarly concluded that the oral drug regimens were associated with relapse of melioidosis. Oral amoxcibiliin-clavulanic acid (coamoxiclav) demonstrated significantly related to risk of relapse; more frequent by 3.3 times than oral combination regimen of chloramphenicol, doxycycline, and cotrimoxazole. The longer duration of oral regimen the lower the risk of relapse by 1.6-fold (Chaowagul et al., 1993). Every 4-week increased the hazard ratio decreased by 29% (Limmathurotsakul et al., 2006).

2.1.5 Treatment of Melioidosis

This part of the literature review aims to gather melioidosis treatment information some of which will be later used as model parameters. Keywords used in the search were melioidosis in combination with Meropenem, Ceftazidime. Then all search results were short listed by the inclusion criteria. Following are the eligibility criteria for the selection of studies:

- Study design: Randomized control trial, case-control and cohort study
- Population: Severe melioidosis infection in adult
- Treatment: comparison between Ceftazidime and/ Meropenem
- Outcomes of treatment: in-hospital mortality rate
- Languages of publication: English
- Sample size: any

Unpublished reports are allowed to be used in the analysis. No exclusion criteria were set for this systematic review because all evidences can be useful for the analysis. The data from selected studies then will be extracted.

The use of Ceftazidime and Meropenem

- Ceftazidime is a broad-spectrum cephalosporin antibiotic group for parenteral administration. Meropenem is a cabapenem antibiotics and is also a broad-spectrum, beta-lactam anibiotic. Both drugs' microbiological mechanism is similar action which is bactericidal (Glaxo Smith Kline 2011: online, Leelarasamee et al., 2008) .

Ceftazidime is generally well tolerated. Around 2% of patients might have inflammation at injection site, hypersensitivity to drug e.g. rash and diarrhea (GSK 2011: online). From two meropenem studies conducted in Thai population, one found no significant adverse reaction (Leelarasamee et al., 2008) and another study found that of 16 healthy volunteers 5 had experienced of back pain, dizziness, headache, pain at injection site (Thamlikitkul et al., 2010).

- Ceftazidime and Cabapenem (Imepenem and Meropenem) were recommended treatment for acute phase of severe melioidosis in many melioidosis treatment guidelines Estes, Dow, Schweizer and Torres, 2010; Cheng, Inglish, 2010; West and Limmathurotsakul, 2009). The guideline relatively consistent with Thai National Essential Drug List Number 4 (2009) with additional indication for the two drugs. Apart from melioidosis Ceftazidime is also listed as a treatment for *P. aeruginosa*. While Meropenem is specifically indicated for multiple drug resistant (MDR) melioidosis and should be prescribed with the drug sensitivity test result or according to infectious disease expert's recommendation. This may be because of high price of Meropenem.
- In practice at Sappasitprasong hospital Ceftazidime has been the recommended for first-line therapy for suspected or confirmed melioidosis since 1989 after the RCT conducted by White et al. (1989) showing that Ceftazidime halved mortality rates compared with a conventional drug regimen (combination of chloramphenicol, doxycycline, and trimethoprim-sulphamethoxazole) (Limmathurotsakul et al., 2010). On the admission, clinicians will use combination of medical history, demographic information (live in endemic areas and expose to soil), baseline diseases e.g. diabetes and clinical signs and symptoms to judge if the patient is suspected to have melioidosis then further decide what specific diagnostic test need to be done and which parenteral antibiotics to be prescribed.

Effectiveness of Ceftazidime and Meropenem

- Cheng and Currie (2005) reported Ceftazidime reducing mortality rates compared to other drugs in 6 clinical trials summarized in table 2.2 below. From the results

below, Ceftazidime showed a benefit in mortality reduction over other combination treatments (chloramphenicol–doxycycline–TMP-SMX; known as conventional therapy) in severe disease. Ceftazidime was associated with a 50% reduction in mortality, from 74 to 37% in Thai adults.

Table 2.2 Summary of clinical trial compared Ceftazidime with other antibiotics regimens

Regimen (dose, mg/kg/day)	Duration (days)	No. of patients		Outcomes measures (%)	
		Enrolled	Culture confirmed	Treatment failure	Mortality
Ceftazidime (120) vs chloramphenicol (100), doxycycline (4), and TMP-SMX (10/50)	At least 7	161	34 vs 31		37 vs 74
Ceftazidime (100) and TMP-SMX (8/40) vs (100), doxycycline (4), and TMP-SMX (8/40)	10-14	136	27 vs 34		18.5 vs 47
Ceftazidime (120) vs amoxicillin-clavulanate (120/40)	At least 7	379	106 vs 105	39 vs 51	47 vs 47
Ceftazidime (120) vs Imipenem (50)	At least 10	296	106 vs 108	41 vs 20	38 vs 36
Ceftazidime (25) and co-trimoxazole (8/40) vs cefoperazone-sulbactam (100) and co-trimoxazole (8/40)		84	20 vs 20		21 vs 16
Ceftazidime (100) and TMP-SMX (8/40) vs Cefoperazone-sulbactam (25/25)	14219		51 vs 51		14 vs 18
Ceftazidime (120) vs Ceftazidime (120) and TMP-SMX (10/50)	10 days	449	118 vs 123		No significant difference

Sources: Cheng et al., 2005

- Retrospective study of selected melioidosis cases treated with Meropenem compared with Ceftazidime in the Royal Darwin Hospital, Australia from August 1997 to July 2003 carried out by Cheng et al. (2004). The findings were that among 68 admissions treated with Meropenem (63 patients, 5 patients relapsed), mortality was 19% (8 death from melioidosis and 4 due to unrelated causes). There were 165 admissions treated with Ceftazidime (154 patients with 11 relapses), the mortality rate was 18% (16 were due to melioidosis and 12 due to underlying disease). This showed no difference in reducing mortality rate. There is however a strong potential bias here, in that Meropenem is often prescribed to patients who are more severely ill. However, in a sub-group analysis of severe sepsis where Meropenem was associated with a much lower mortality than Ceftazidime (25% versus 75%, $P < 0.001$).

- Smith et al (1994) conducted an *in vitro* study of *B. psuedomeliei* sensitivity to Ceftazidime and carbapenem antibiotics (Meropenem, imipenem) and reported that the bacteria which are resistant to Ceftazidime were susceptible to carbarpenems. Using time-kill kinetic studies, Ceftazidime did not show "significant" bactericidal activity whereas Meropenem was bactericidal (99.9% kill) within 6 hours.
- Simpson et al (1999) conducted a randomized controlled trial to compare efficacy of high-dose intravenous imipenem (carbapenem antibiotics) and Ceftazidime in Thai adult patients with suspected acute, severe melioidosis. Of the 296 patients, 214 patients had culture-confirmed melioidosis. Overall mortality of melioidosis patients was 36.9% but not significantly different between the two groups. However, this trial found a significant difference in treatment failure after 48 hours in patients with Ceftazidime arm (*P 0.011*). The author also concluded that imepenem can be considered an alternative to Ceftazidime.
- Choawakul (2010) summarized that mortality of relapse episodes is similar to the primary infections. The same treatment guideline should be applied for severe relapse cases of melioidosis. Relapses were found to be associated with poor compliance with eradication drugs rather than the underlying disease of patients. For relapse prevention, the patients should be prescribed with long term oral antibiotic.

2.2 Economic evaluation literature:

Cost-effectiveness analyses of the melioidosis drugs have not been investigated before. Therefore, published papers regarding economic evaluation of the drugs of interests for severe infectious diseases which share similar clinical course with melioidosis were searched for instead. Keywords of cost-effectiveness in combination with Meropenem and/ severe infection were used.

- Edwards, Campell and Plumb, 2006 and Edward, Wordsworth and Clarke, 2010 conducted cost-utility analysis of Meropenem with impipenem plus cilastatin and with piperacillin/tazobactam in the treatment of severe infections in intensive care

wards in the United Kingdom. Both of the studies were done taking the UK National Health Service perspective, where the costs associated with the antibiotics being compared lie within a hospital care setting.

A Markov model was used to illustrate the course of patients' prognosis and patient management in the ICU. Model parameters categorized in to 5 types: common (can apply to both drugs), efficacy (specified to each drug), utility, drug cost and service cost. The utility and cost inputs were obtained from published data.

There were two major categories of cost taken into the analyses in both studies. The first category was bed-day ward costs in each ward that patients were transferred to during the course of treatment (e.g. the ICU, general ward). The second category was the drug costs.

Probabilistic sensitivity analysis (PSA) was performed to assess the impact of uncertainty in parameters on the results using a Monte Carlo Simulation. Beta distributions were assigned to probabilities as their values are between 0 and 1. The limit applied on the effectiveness data were derived from 95% confidence intervals calculated in the systematic review. Where the reference/ original data did not measure the uncertainty around mean values such as drug administration quantities or the daily cost data, the authors varied the values within ±50% of the mean value. Lengths of stay normally have a skewed distribution and always starts from 0 hence a gamma distribution was employed. (Edwards, Wordsworth and Clarke, 2010)

The results were presented in terms of incremental cost per QALY gained. On the cost-effectiveness plain, 10,000 estimates of the ICER were concentrated in the quadrant 3 indicating dominance of Meropenem. In the UK setting, it was concluded that Meropenem was more effective and less expensive than imipenem in both studies.

- Riewpaiboon and Health Intervention and technology Assessment Program (2009) conducted cost analysis and created a standard unit cost in community hospital and general/regional hospital. The two costing methods were used, a

standard method and a weight procedure method. The standard unit costs are categorized in direct medical cost and indirect medical cost to patient (e.g. traveling cost) of 3 main health care institutes (health center, community hospitals, general/regional hospital) (Riewpaiboon. 2009, pp. 4-13). This unit cost will allow the economomic evaluation results can be generalized and comparable in Thai context.

- Decision rule whether the medical intervention is cost-effectivness, the WHO uses 1-3 times GDP per capita as a threshold to consider that health an intervention is cost effective (WHO-CHOICE 2005; HITAP 2007).

In summary, all suspected melioidosis will be included in the model as according to the hospital practice. The treatment failure will be identified in the model allow the model to include the consequences both cost and outcomes occur and can be a differentiate point between the two drug. The current evidences regarding mortality rate in patients with baseline conditions such as diabetes and abscesses shown indifferences but hardly to conclude therefore the underline diseases will not take in to account in the model. The motality rate reported in the randomised controlled trial will be used as model parameters.

For cost-effectiveness comparison, the cost of drug and hospitalization are considered to be sufficient. In health care provider's perspective and will take the human capital approach to decide whether the interventions are cost-effectiveness. In this analysis will conservatively evaluate if Meropenem is a cost-effective intervention and if it should be adopted to replace Ceftazidime, hence the lower limit of WHO cost-effectiveness threshold; 1 GDP per capital will be used although the range of 1-3 GDP is accepted to be cost-effective by WHO-CHOICE guideline.

CHAPTER III
RESEARCH METHODOLOGY

3.1 Research Design

This economic evaluation is a modelling-based cost-effectiveness analysis to compare both cost and health outcomes of the two interventions; Meropenem and Ceftazidime.

A decision analytic model will be used as an analytic framework in this study. The model allows us to illustrate the course of action and take important data such as effectiveness, resource use, cost data into account and examine the impact of uncertainty due to incompleteness of data. Then we can identify the most cost-effectiveness option by comparing the expected value of alternatives. The structure of the model and also estimates of input parameters are created and derived based upon best current evidences available in published literatures. This inevitably contain uncertainties, hence the sensitivity analysis is needed to assess the impact of uncertainties on the analysis result (Drummond and McGuire., 2007).

Decision analytic model: Decision tree

A decision tree is appropriate to represent the management of severe melioidosis. The decision tree was developed to assess the alternative treatments (Ceftazidime, Meropenem) and is illustrated in figure 1. The branches start off with the initial decision node then follow with a series of probability nodes. At the end of each pathway two sets of outcome are calculated; health outcomes (number of life year saved) and resources consumption expressed via monetary measure of cost.

Perspective

This cost-effectiveness will be done using a health care provider's perspective. Therefore, direct medical cost of health care resources consumed in the treatment of severe melioidosis will be taken into account.

Time horizon

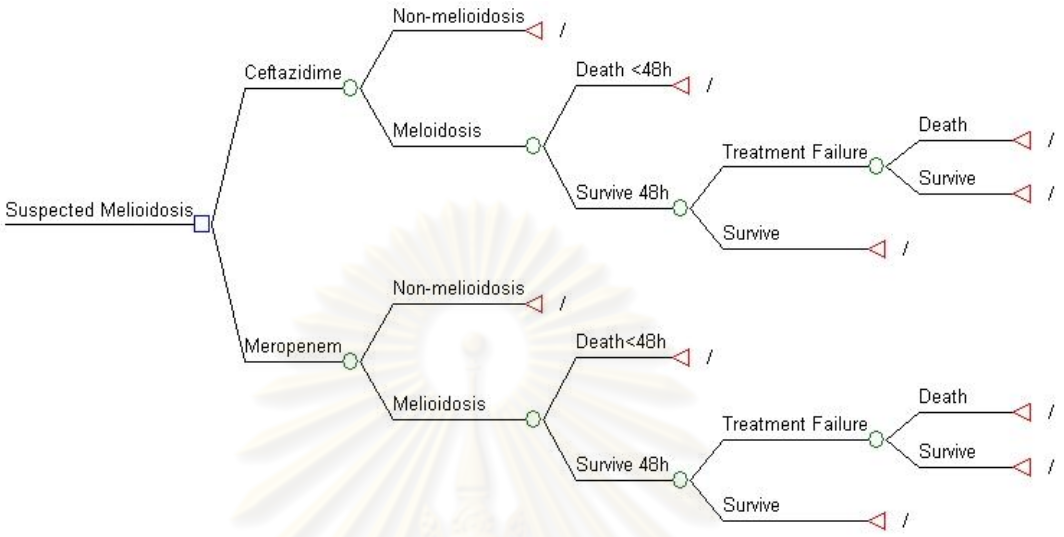
The time span captured in the model starts from admission until discharge from the hospital or death as the purpose of parenteral antibiotic drugs (Ceftazidime and Meropenem) is to reduce in-hospital mortality. The measure of effectiveness however is the number of life years saved which is measured using average life expectancy at the age of admission. This is discounted by a standard 3% (Health Intervention and Technology Assessment Program (HITAP), 2007 pp. 129).

Structure of the model

Structure of the model (Figure 3.1) was created based on natural course of severe melioidosis and current disease management practice. The decision tree is composed with one decision point and four chances of possible occurrences.

- The decision point is where physician decide to prescribe Ceftazidime or Meropenem to all suspected melioidosis infection. At the admission, clinicians will treat all suspected cases with parenteral antibiotics because signs and symptoms of melioidosis are similar to other febrile diseases and cannot be determined by clinical diagnosis alone.
- The first chance node following treatment is where patients have either melioidosis infection or an alternative cause of illness, as confirmed by laboratory culture.
- For patients with confirmed melioidosis, there is a probability that these will die within the first 48 hours. Deaths within this time period are generally associated with extreme severity of illness and not treatment failure, although differences in the efficacy of treatment in this period have been observed.
- Patients who survived after 48 hours will face with chance of treatment failure or success.
- The last chance node is for survival after treatment failure.

Figure 3.1 Decision tree of severe melioidosis treatment



Model assumptions:

1. All probabilities of events were adopted from one randomised controlled trial titled "Comparison of Imipenem and Ceftazidime as Therapy for Severe Melioidosis" by Simpson (1999). Therefore the effectiveness of imipenem will be used to represent Meropenem's effectiveness because of Meropenem's effectiveness is not yet available. Imipenem and Meropenem are in the same class of beta-lactam antibiotics, carbapenem, and shown fast time-kill profile to *B. psuedomeliei*. In addition, from expert opinion both drugs have shown similar effectiveness in clinical use.
2. Treatment failure was defined as one or more of the following: all death occurring after 48 hours; patients' clinical sign and symptoms worsen and development of shock after more than 72 hours; fever and the clinical conditions were not improving after 14 days of IV treatment; *B. psuedomelliei* persisted for more than 7 days after starting treatment. Some of the treatment failure patients had to switch the study drug. Patients who were initially treated with Ceftazidime would be switched to receive Meropenem. Patients who started with Meropenem would continue to receive Meropenem. This assumption reflects current practice of treatment failure management.

3. Non-melioidosis patients are assumed to be treated with Meropenem/ Ceftazidime until receiving the culture result and then treated with other antibiotics which corresponded to the culture result. Health outcome of treatment in this group was not taken into consideration because it was confounded with other subsequent antibiotics. However, the cost incurred during the initial period of treatment was related to the decision to treat with Meropenem/ Ceftazidime hence the cost was include in analysis.
4. Apart from duration of treatment of the drugs and length of hospitalization which are used to identify the differences of cost-effectiveness between the two drugs, the other treatments or procedures are assumed to be similar between the two groups. This is because the baseline characteristics of the two are similar.
5. The antibiotic resistant and adverse events that may occur from each drug are not taken into account in this model. This will be considered as a limitation of the model in this study.
6. All patients are assumed to stay in one in-patient ward until successfully treated and discharged or die.
7. Melioidosis patients often have other co-morbidities such as diabetes and renal impairment and are assumed to have no difference in mortality rate in the model. This is because there is very limited data on mortality differences in patients who have a co-morbidity and those who have not. 3.2 Data Collection

3.2.1 Effectiveness Data

As detailed in the literature review, only a single trial was identified that compared the effectiveness of treatment with Ceftazidime to a carbapenem antibiotic (Simpson et al. 1999).Data from this trial were used for the base-case analysis in this analysis. The crude probability of death, standard error and range of 95% Confidence Interval from the clinical trial were calculated by the following formulas.

$$\boldsymbol{Probability\ of\ Death}\ (\boldsymbol{p}) = \frac{No\ of\ death}{No\ of\ subjects}$$

$$\boldsymbol{Standard\ Error}\ = \sqrt{[\mathrm{p}(1-\mathrm{p})\ \div\ \mathrm{n}]}$$

$$\mathbf{95\%}\ \boldsymbol{Confidence\ Interval}\ = (p \pm (1.96\ x\ \sqrt{[p(1-p)\ \div\ n]}$$

Obtaining expert opinions

Meropenem is a relatively new treatment of severe melioidosis, which explains the absence of randomized control trials for this drug. Therefore to supplement the reference case that used effectiveness data relating to imipenem, further estimates on the potential effectiveness of Meropenem were obtained form expert opinion.

The expert opinion form (appendix B) includes brief information about the reference study and predetermined probabilities extracted from the RCT. This was sent to 4 experts in the field. The experts were asked to evaluate the probabilistic parameters (probability of death) in each stage of the model and to provide their opinions.

3.2.2 Cost Data

The analysis will be done taking the health care provider's perspective hence only direct medical cost incurred during hospitalization will be considered. There are two main elements in costing; the assignment of unit cost or price and measurement of quantities of resource use (Drummond, 2005).

1. Unit Cost

Different settings may have different variable costs and ideally the specific setting unit cost should be calculated. To make the study result generalizable and beneficial to other regional hospitals in Thailand, the unit cost will be obtained from secondary data from a "Standard Cost List for Health Technology Assessment" developed by Assoc. Prof. Arthorn Riewpaiboon and HITAP (Health Intervention and technology Assessment Program). This can be accessed online via http://www.hitap.net/costingmenu. This standard unit cost analysis was conducted in three regional hospitals therefore this is assumed to be representative of Sapprasithiprasong hospital.

The drug cost are obtained from Drug and Medical Supply Information Center (DMSIC). This is available via online access; http://dmsic.moph.go.th/price.htm.

Because the standard unit cost was calculated from the cost data in year 2009, therefore the cost per patient per hospitalization will be converted and reported in 2011 Baht using the consumer price index (CPI).

Cost in Year 2011= Cost in Year 2009 x [CPI_{2011} / CPI_{2009}]

2. Measurement of quantities of health care resource

Health care resources used in management of severe melioidosis included the main cost drivers, hospitalization cost and drug cost. The quantities of resources consumed are obtained from either retrospective patient level data from Sapprasithiprasong hospital from years 1997 – 2006 or published data.

The quantities parameters to be collected are:

a. Hospitalization costs, which are a function of Length of stay and include labor, capital and medical supplies costs)
b. Antibiotic treatment costs, which are a function of the duration and dosage of treatment

3. Cost calculation

Total cost calculated in this study is limited to cost of hospitalization and cost of drugs. Although this cost does not represent the true cost to health care providers, this cost is sufficient to provide estimate the incremental cost of treatment with Meropenem and therefore to assess whether Meropenem is more cost-effectiveness than cefatzidime.

The quantity of resources used per patient is multiplied with standard unit cost to get the total cost per hospitalization per patient as in the formula below.

Cost per patient per hospitalization = (#Length of Stay x Cost per hospitalization day) + (#Duration of therapy x Cost of drug per day)

Where;

- **Cost per hospitalization day** = In-patient bed unit cost +
  In-patient nursing services unit cost +
  In-patient doctor services unit cost +
  IV drug administration unit cost
- **Ceftazidime Drug cost** = Cost of primary drug +
  Cost of secondary drug for treatment failures

  Cost of primary drug = (*Cefazidime cost* x *Duration primary treatment*)

  Cost of secondary drug = [*Prob. of switch* x (*Meropenem cost* x *Duration second. treatment*)] + [(1- *Prob. of switch*) x (*Ceftazidime cost* x *Duration second. treatment*)]
- **Meropenem Drug cost** = Meropenem cost x Duration of treatment

3.3 Data Analysis

3.3.1 Cost-Effectiveness Analysis

Cost-effectiveness analysis compares both cost and outcomes of the alternatives interventions. The health outcome from the RCT (mortality) will be valued as Life Years Saved (LYS). Life years are the most widely used measure of health benefit when the major gain from an intervention is extra life expectancy. (Drummond and McGuire, 2007 pp. 28) Although in reality the value placed on a life year can vary depending on the quality of life during that year, this analysis does not account for the impact of quality of life. For survivors of severe melioidosis, the life year gained is assumed to be a normal healthy life and at full health. The number of life years saved is discounted at 3% as in standard methods (Drummond, 2007; HITAP). Life year saved/gained can be calculated by the formula below.

$$\text{Discounted Life Year Saved (per one life saved)} = \frac{vLY*(1-(1+r)^{-LE}}{r}$$

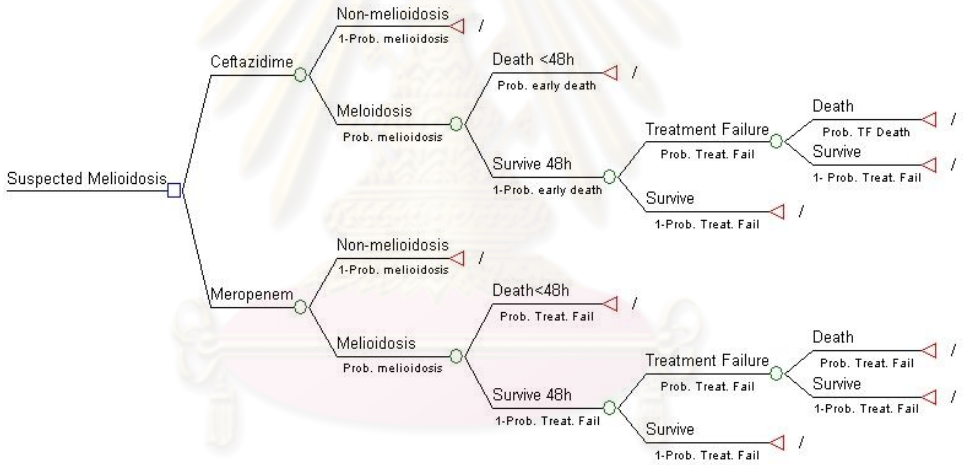
Where;

- vLY = value of each life year; assumed to be normal healthy life which is equal to 1.
- rate= discount rate (3%)
- LE = life expectancy calculated using avergae patient age and the life expectancy obtained from WHO Life Table (2008).

Calculating expected value

The expected value of each arm is calculated firstly by multiply probabilities with value of outcomes; life year saved (LYS) then combining all values values for each alternative; Expected Value of each drug = $\sum_{i=1}^{n} Prob.(X_i)\ x\ LYS(X_i)$

Figure 3.1: Expected Value Calculation



Expected Value Calculation

Non-melioidosis =	[(Prob. of non-melioidosis) x (LYS)] +
Melioidosis & died within 48 hours =	[(Prob. of melioidosis) x (Prob. of Death <48h) x (LYS)] +
Treatment Failure and died=	[(Prob. of melioidosis) x (Prob. of Survive 48h) x (Prob. of Treat. Fail.) x (Prob. of Death) x (LYS)] +
Treatment Failure and survived =	[(Prob. of melioidosis) x (Prob. of Survive 48h) x (Prob. of Treat. Fail.) x (Prob. of Survive) x (LYS)] +
Survive without treatment failure =	[(Prob. of melioidosis) x (Prob. of Survive 48h) x (Prob. of no Treat. Fail.) x (LYS)]
=	Expected Value (LYS)

Then calculate Cost-Effectiveness Ratio (CER):

Cost-Effectiveness Ratio = Cost / LYS

Result presentation

The analysis will be presented taking two approaches to interpret the results for decision-making purposes, the incremental cost-effectiveness ratio and a probabilistic measure of an intervention's cost-effectiveness (Morris, Devlin and Parkin., 2007 pp. 252).

1) Incremental Cost-effectiveness ratio (ICER) represents the cost per additional life year saved.

$$\text{ICER} = \frac{Cost_{Mero.} - Cost_{Cef.}}{LYS_{Mero.} - LYS_{Cef.}}$$

Then ICER will be plotted on the cost-effectiveness plane (Figure 3.2). The cost-effective plane is divided into four quadrants to show all possible comparison of cost and effects, on the vertical and horizontal axis, respectively.

The Ceiling Ratio and Decision rule

The ICER alone may not be very useful in making recommendations over one intervention over another, as a measure of comparison is required to decide if the ICER represents a cost-effective intervention. To overcome this, the cost-effectiveness ratio threshold or ceiling ratio will be applied. This threshold is the level to indicate that the intervention is considered to be cost-effective. This level is represents the decision makers' willingness to pay for an additional unit of effectiveness (Morris, Devlin and Parkin., 2007 pp.255). The decision rules are:

If the intervention is more effective and higher cost, this can be considered cost-effectiveness when the ICER is less than the threshold/ ceiling ratio(R_c); $\frac{\Delta C}{\Delta E} < Rc.$

The threshold/ ceiling ratio from WHO cost-effectiveness below will be used as the decision rule.

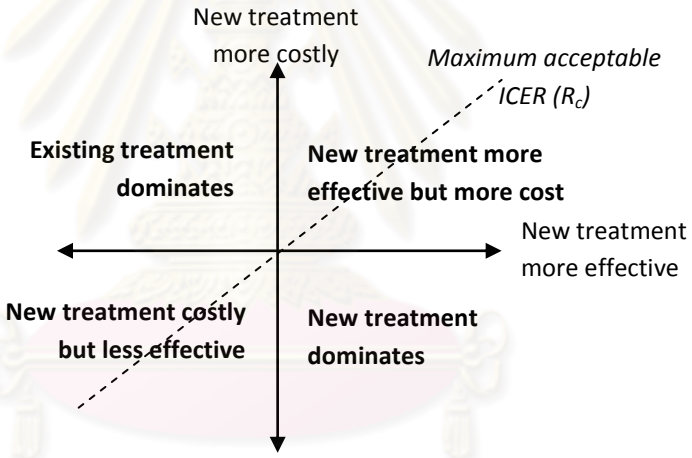
Level of cost-effectiveness	GDP per capita
Very cost-effective	< 1
cost-effective	1-3
not cost-effective	> 3

Source: WHO-CHOICE, 2005: online

The GDP per capita of Thailand is approximately 100,000 Baht. Therefore, the intervention will be cost-effectiveness when the incremental cost-effectiveness ratio (ICER) falls in between 100,000 to 300,000 Baht (HITAP, 2007).

The decision rule is illustrated in figure 3.2 below:

Figure 3.2 The cost-effectiveness plane and decision rule



Source: Drummond and McGuire, 2007 pp. 174

2) Probabilistic approach

Because the parameters used in this cost-effectiveness analysis are from secondary data surrounded with uncertainties so the result, it is difficult to conclude for certain that either drug is cost-effective; instead the results are expressed by stating the probability that the superior treatment is cost-effectiveness. Therefore the cost-effectiveness acceptability curve (CEAC) will be used to indicate the probability that each drug is cost-effective relative to the threshold. The vertical axis is the probability that the intervention is

cost-effective for all possible values of the ceiling ratio, R_c at the horizontal axis.

3.3.2 Sensitivity Analysis

The result obtain from cost-effectiveness analyses based on decision analytic modeling contains four key sources of uncertainty; methodological (different methods selected to value cost and health outcomes yield different result), parameter uncertainty, modeling uncertainty (structure and process) and the generalisability (ability to transfer results to other setting). The sensitivity analysis is a way to handle parameter uncertainties and show how sensitive results are when parameters change within plausible range.

This study will take an extensive set of sensitivity analysis because the parameters were not directly observed from real treatment course. Hence, the ICER result will be tested by one way sensitivity analysis and probabilistic sensitivity analysis.

1. One Way Sensitivity Analysis

This type of sensitivity analysis tests how results changes when varying one parameter within a plausible range. The relevant range for the probabilistic parameters will be the 95% confidence interval using the sample mean and standard deviation. If it is not feasible to use statistical range, a fixed percentage representing a plausible range for the parameter will be adopted. The One way sensitivity analysis allows us to test the result for specific scenarios of interest:

1) Changing 3 key probabilities in the decision tree: death rate within 48 hours, death after treatment failure, incidence of confirmed melioidosis infection

The treatment effectiveness is a key issue in the analysis therefore early mortality and treatment failure rates are included in the one way sensitivity analysis. Regarding the incidence, higher incidence of the disease, will lead to a more expensive drug being even more cost-effective. If on the other hand

the incidence is low and many of the patients receive the more expensive treatment unnecessarily, this will reduce the cost-effectiveness of the drug.

2) Scenario for reduced Meropenem drug cost

New drugs tend to be more expensive and more effectiveness than those they aim to replace. By varying the cost of the new drug it is possible to identify the cost at which it may become not cost-effective when compared to the threshold of 100,000 Baht per one life year saved.

3.3.3 Probabilistic Sensitivity Analysis

This type of sensitivity analysis is used to estimate results when varying all parameters simultaneously using Monte Carlo simulation. Parameters will be assigned a distribution and range. The simulation will randomly select a possible value within the range and distribution and recalculate the incremental cost effectiveness. This can then be presented as a scatter plot on the ICE plane and summarized by calculating the proportion of iterations where the ICER was below the decision threshold.

3.4 Limitations of the Study

3.4.1 Cost of treatment

There are two elements in cost calculation, unit cost and quantity of resources used. The quantity of health care resource consumed are not directly collected from patient level data, therefore whole health care resources consumption for the treatment are not entirely represented in the result.

The unit cost used is from the standard unit cost developed by Assoc. Prof. Arthorn Riewpaiboon and HITAP (Health Intervention and technology Assessment Program) which is calculated based on an assumption that regional hospitals operate efficiently, thus the unit costs are possibly lower than the less

efficient operate hospitals. Therefore, the cost reported in this analysis may not precisely represent the treatment costs incurred at Sapprasithiprasong hospital.

3.4.2 Effectiveness of treatment

Ideally the cost-effectiveness evaluation should be done with the data from randomised controlled trial that directly compare the drugs of interest. Because Meropenem has only recently been used for severe melioidosis treatment in Thailand there is only limited clinical effectiveness evidence. However, the uncertainties surrounding these parameters will be tested by probabilistic sensitivity analysis (PSA).

CHAPTER IV
RESULTS

4.1 Systematic review

The literature review searching for papers on severe melioidosis treatment identified 657 studies that contained the relevant keywords. These were shortlisted to 4 papers that have met the inclusion criteria of systematic review process. Table 4.1 shows the summary of published paper obtained.

Table 4.1 Characteristic of studies obtained from systematic review

Study 1: Cheng AC et al. (2004)	
Research Type	Retrospective observational
Intervention	Group 1: Meropenem (1 gm or 25 mg/kg every 8 hours) in combination with trimethoprim/ sulfamethoxazole Group 2: Ceftazidime (2 gm every 8 hours)
Sample size	217 (Meropenem = 63, Ceftazidime = 154)
Outcomes	Mortality rate
Study location	Patients with severe melioidosis treated in Darwin hospital, Australia
Study period	August 1997 to July 2003
Results	No difference in overall mortality rate between the two groups (19%, 18% in Meropenem and Ceftazidime group) but there was statistically significant difference in sub-group analysis. In sepsis patients, Meropenem showed a much lower mortality rate; 25% compare to 76% in Ceftazidime treatment group.

Study 2: White NJ et al. (1989)

Research Type	Open, prospective, randomized trial
Intervention	Group 1: Ceftazidime (120 mg/kg/day) Group 2: Conventional therapy; Chloramphenicol (100 mg/kg/day), Doxycyclin (4 mg/kg/day), Trimethoprim (10 mg/kg/day), Sulphamethoxazole (50 mg/kg/day)
Sample size	161
Outcomes	Mortality rate
Study location	Sappasithprasong hospital, Ubon Rachathani
Study period	NA
Results	Ceftazidime treatment's mortality rate was much lower than conventional treatment, 37% versus 74% (*p=0.009*)

Study 3: Suputtamongkol et al. (1994)

Research Type	Open label, randomised control trial
Intervention	Group 1: Ceftazidime (120 mg/kg/day) Group 2: Amoxicillin/Clavulanate
Population	212 (Ceftazidime = 106, Amoxicillin = 106)
Outcomes	Mortality rate
Study location	Ubon Rachathani
Study period	NA
Results	Overall mortality rates were similar for both treatment groups; 45% in Ceftazidime group and 39% in the amoxicillin/ clavulanate group.

Study 4: Chierakul et al. (2005)

Research Type	Randomised controlled trials
Intervention	Group 1: Ceftazidime (120 mg/kg/day) Group 2: Ceftazidime + Trimethoprim-Sulfamethoxazole (TMP-SMX)
Population	449 (Khonkan: 232, Ubon Rachathani: 217)
Outcomes	In-hospital mortality rate
Study location	Khonkan and Ubon Rachathani
Study period	1999 - 2003
Results	There were no different in overall mortality rate (25.1%, 26.6% in Ceftazidime and Ceftazidime + TMP-SMX).

Of the four studies, three were excluded because they were comparison Ceftazidime and other traditional regimens rather than Meropenem. One paper from Cheng AC et al. (2004) retrospectively studied to compare the outcome of Meropenem and Ceftazidime for the treatment of severe melioidosis. This is the only published paper available that reported a direct comparison of the pair of antibiotic drugs of interest (Meropenem and Ceftazidime). This study, however, contained a selection bias that Meropenem was selected to treat more severe patients as according to the Australian treatment guidelines. Unfortunately Meropenem was also not given as monotherapy but administered with trimethoprim/ sulfamethoxazole hence the result may also contained the effect of combination drugs. In addition some of patients included in analysis as in Meropenem group were patients whom were first treated with Ceftazidime. Therefore this study was excluded and not used in the analysis because it contains major biases.

In the absence of effectiveness data for Meropenem, however from White (2003) and expert opinion suggested that Meropenem is probably equipvalent to Imipenem. It was decided to use effectiveness data for imipenem as a substitute. Imipenem shares the same pharmacokinetics characteristics and has a similar time-kill profile as Meropenem. Imipenem and Meropenem are in the same class of beta-lactam antibiotics, carbapenem, with a broad spectrum of antibacterial activity, and is routinely used for the treatment of severe melioidosis. Some differences between the two drugs have been obsevered as reported in Cheng et al. (2004), that Meropenem has its advantage over imipenem because it is not associated with seizures. Therefore, the systematic review inclusion criteria were expanded to include imipenem.

After changing the criteria, one randomised controlled trial conducted by Simpson et al. (1999) was found. This trial compared imipenem with Ceftazidime in the treatment of severe melioidosis at Sapprasithiprasong hospital in the years 1994 to 1997 (Table 4.2). Given the RCT study design and the similarities between imipenem and Meropenem, it was concluded that this would be the best representation for Meropenem's effectiveness when compared with Ceftazidime in treating severe melioidosis. Therefore, this trial is used as the main source of evidence from which all parameters are extracted.

Table 4.2: Characteristic of the randomised controlled trial "Comparison of Imipenem and Ceftazidime as Therapy for Severe Melioidosis" by Simson et al. (1999)

Research Type	Randomized controlled trial
Intervention	Group 1: Imipenem (1 gm every 8 hours) Group 2: Ceftazidime (2 gm every 8 hours)
Sample size	214 (Imipenem = 108, Ceftazidime = 106)
Outcomes	Mortality rate
Study location	Sappasithprasong hospital, Ubon Rachathani
Study period	July 1994 to November 1997
Results	Overall mortality rate in the two groups are 36.1% in imipenem group and 37.7% in Ceftazidime group and was not statistically significant. However, the treatment failure was significantly different. Imipenem group shown much lower treatment failure rate at 20.3% compared to 41.3% in patients treated with Ceftazidime.

4.2 Baseline Characteristics

The baseline data in this study were captured from the randomized controlled trial comparing between Imipenem and Ceftazidime as treatment for severe melioidosis conducted by Simpson (1999). Baseline characteristics to be used in decision analytic model based on patients characteristics in this clinical trial. 56.5% of the patients are male median age is 52 years old. Median of fever was 10 days. 62% - 70% of patients have septicemia. There are no differences in baseline disease in the two treatment groups.

Table 4.3 Baseline characteristics

Characteristic	No. (%) of recipients		*P* value
	Imipenem (n=108)	Ceftazidime (n=106)	
Male	61 (56.5)	57 (53.8)	.69
Age in years: median (range)	52 (18-82)	51 (21-76)	.91
Duraton (d) of fever, median (range)	10 (1-90)	10 (1-150)	.32
Prior antibiotic therapy (this episode)	72 (66.7)	80 (75.5)	.16
Type/ site of infecton			
Septicemia	62 (57.4)	70 (66.0)	.25
Lung	60 (55.6)	59 (55.7)	1.0
Hepatic or splenic abscesses	29 (26.9)	30 (28.3)	.81
Skin or soft-tissue infection	21 (19.4)	36 (34.0)	.02
Bone or joint infecton	11 (10.2)	10 (9.4)	.85
Positive pour-plate culture	28 (28.0)	34 (35.1)	.36
Fever (temperature of >37.5° C)	61 (56.5)	62(58.5)	.77
Hypotension (systolic blood pressure of <90 mm Hg)	13 (12.0)	10 (9.4)	.54
Impaired consciousness level	22 (20.4)	21 (19.8)	.92
Dyspnea	43 (39.8)	45 (42.5)	.69
Jaundice	29 (26.9)	23 (21.7)	.38
Hepatomegaly	48 (44.4)	49 (46.2)	.79
Splenomegaly	15 (13.9)	13 (12.3)	.72

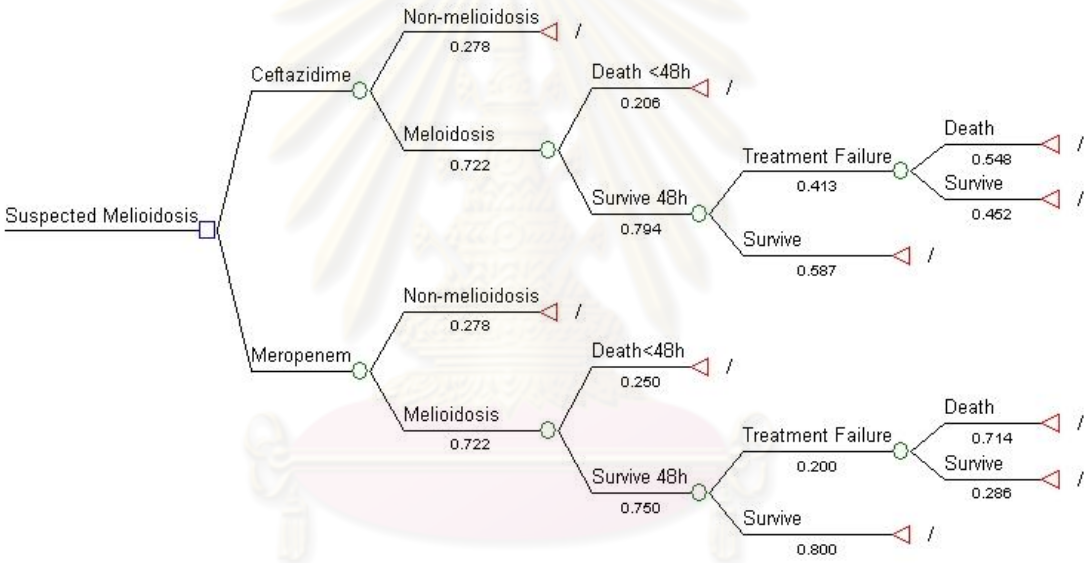
Source: Simpson et al. (1999)

4.3 Decision Analytic Model

4.3.1 Decision Tree

The decision tree is representing the course of severe melioidosis treatment and its outcomes - whether the patient will be successfully treated and survive or die. Time horizon of this model is hospitalization period from admission until discharge. The outcome of interest is in hospital mortality. Figure 4.1 is the decision analytic model to simulate the course of severe melioidosis management.

Figure 4.1 The course of treatment and outcomes of Ceftazidime and Meropenem



In practice, parenteral antibiotics (Ceftazidime or Meropenem) will be provided to all suspected melioidosis infection. The decision tree will branch off with choice of treatment which is provided to every suspected melioidosis infection patient. Then all suspected cases will contain the chance of either infected by *B. pseudomellei* or other type of bacteria. This will be confirmed by blood/respiratory secretions/ urine/ throat, pus, surface swab culture. This laboratory culture results can be obtained at least 24 to 48 hours or more. (Wuthiekanun et al., 2004) At this stage, all non-melioidosis infection will be treated with cefazidime/ Meropenem until receiving the diagnosis result which will take on average 3 days (range 2-4 days).

Confirmed melioidosis patients can die in the first 48 hours or survive and continue his/ her treatment. Patients who survive first 48 hours will have chance to have treatment failure or fully recover and discharged from the hospital. In the treatment failure group some of the patients may be required to switch the antibiotic drugs. Patients who are not facing treatment failure will be treated with the primary treatment (first antibiotic provided) until they recover or die.

4.3.2 Model Parameters

From the published trial, 4 categories of parameters were extracted - epidemiology parameters, treatment effectiveness parameters, length of stay and duration of therapy. These parameters are used in the corresponding branch in the decision analytic model. Table 4.4 details the list of parameters in the model.

Table 4.4 Summary of model parameters

Parameter	Original data		Source of data
a. Common epidemiology parameter:			
▪ Patients with confirmed melioidosis infection	0. 723	SE = 0.26	Simpson et al. (1999)
b. Effectiveness parameters:			
▪ **Ceftazidime**			
o Death within 48 hours after treatment with Ceftazidime	0.208	SE = 0.039	Simpson et al. (1999)
o Ceftazidime treatement failure	0.413	SE = 0.057	Simpson et al. (1999)
o Ceftazidime treatement failure and died	0.548	SE = 0.089	Simpson et al. (1999)
o Switch Ceftazidime to alternative treatment after treatment failure	0.516	SE = 0.09	Simpson et al. (1999)
▪ **Meropenem**			
o Death within 48 hours after treatment with Meropenem	0.25	SE = 0.042	Simpson et al. (1999)
o Meropenem treatement failure	0.203	SE = 0.048	Simpson et al. (1999)
o Meropenem treatement failure and died	0.714	SE = 0.121	Simpson et al. (1999)

Parameter	Original data		Source of data
o Switch Meropenem to alternative treatment after treatment failure	0.714	SE = 0.121	Simpson et al. (1999)
c. Length of stay		*Min-Max (days)*	
o Non-melioidosis	*3*	*2-4*	Wuthiekanun et al.(2005)
o Death within 48 hours	*2*	*1-2*	*Model Assumption*
o Survive without treatment failure in Ceftazidime group	*15*	*2 – 47 days*	Simpson et al. (1999)
o Treatment failure: died and survived both treatment group	*23*	*14 – 29 days*	Simpson et al. (1999)
o Survive without treatment failure in Meropenem group	*15*	*5 –43 days*	Simpson et al. (1999)
d. Duration of therapy			
o Duration therapy with primary antibiotic (first given drug)	*10*	*NA*	Simpson et al. (1999)

4.4 Costs

Originally the quantity of health care resources were obtained from secondary data; the database of Sapprasithiprasong hospital, Ubon Rachathani from year 1997 to 2006. There were 5 set of datasets; admission and treatment, hematology test, biochemistry test, serology test, clinical procedures. All data set were analysed by using STATA 10.

The dataset were merged by using the unique admission code then categorized into 8 subgroups according to the decision models. Many missing data were found which had led to lose large amount of observations. The treatments of Meropenem could not be identified because it was recorded as carbarpenem in the database which implied to be either imipenem or Meropenem. The length of stay, number of hematology, biochemistry, duration of Ceftazidime and carbapenem were identified in each subgroup. These data contained serious selection bias 1,040 patients were treated with Ceftazidime and only 30 cases treated with carbarpenem were identified. In addition, there were a lot of confounding factors and large variations therefore they were not

used in cost-effectiveness analysis and not included in result section. The summarized of discarded data obtained from Sappasitprasong hospital are in Appendix C.

This has led to use length of stay and duration of therapy only from RCT was conducted in Sappasitprasong hospital by Simpson (1999). This will solve the selection bias issue because patients were randomly selected to receive each drug, and baseline characteristics of patients in the two groups were similar. These will allow the comparison the cost and outcomes of comparison drugs are much more reliable.

The cost were calculated by using unit costs from the "Standard Cost List for Health Technology Assessment" developed by Assoc. Prof. Arthorn Riewpaiboon and HITAP (Health Intervention and technology Assessment Program). The cost will be calculated by the following formula:

Cost per patient per hospitalization = (#Length of Stay x Cost per hospitalization day)
+ (#duration of therapy x Drug cost per day)

When;

- Hospitalization day cost contains in-patient bed cost, doctor service cost, nursing service cost and IV administration cost.
- Comparative drug costs are calculated from standard dosage which is 2 mg at every 8 hour for Ceftazidime and 1 mg at every 8 for Meropenem.
- Cost of 50 ml normal saline administered with parenteral antibiotics is not included because it is considered as a common cost in both treatment group and its cost is very low.

4.4.1 Unit cost

Because the standard unit cost was calculated from the cost data in year 2009, therefore the cost per patient per hospitalization will be converted and reported in 2011 Baht by using the consumer price index (CPI). The CPIs were obtained from the Bank of Thailand‘s website; http://www2.bot.or.th.

- **Hospitalization day cost:**

  Cost of hospitalization day is 1,418.40 in 2009 Baht combined with in patient bed (809.71 Baht), medical services (557.73 Baht) and IV administration cost (50.96 Baht). Adjusted for 2011 prices using the CPI Baht:

  $$\text{Cost of hospital stay to 2011 Baht} = 1{,}418.40 \text{x} \frac{109.51}{104.50} = 1{,}486.40 \text{ Baht}$$

- **Drugs cost:**

  Drug costs were obtained from purchasing department of Sapprasithiprasong hospital, for the year 2010. They were adjusted to 2011 Baht as in the following equation:

  $$\text{Cost of Meropnem to 2011 Baht} = 1{,}368.53 \text{x} \frac{109.51}{107.96} = 1{,}434.14 \text{ Baht}$$

  $$\text{Cost of Ceftazidime to 2011 Baht} = 24.61 \text{x} \frac{109.51}{107.96} = 25.79 \text{ Baht}$$

  Drugs cost was different from price quoted in Drug and Medical Supply Information Center (DMSIC) website where Meropenem's price is 900 Baht per 1 gram and Ceftazidime is 26 Baht per 1 gram. The differences will be taken into account during sensitivity analysis.

Table 4.5 Summary of Cost parameteres

Drug cost (2011 Baht):	**Unit cost**	**Daily cost**	**Source**
Ceftazidime (IV; 2gm every 8 hours)	24.61 per 1 gm	154.74	2010 purchasing price, Sapprasithiprasong hospital
Meropenem (IV; 1gm every 8 hours)	1,368.53 per 1 gm	4,302.42	2010 purchasing price, Sapprasithiprasong hospital
Cost of Hospital stay (includes capital, material and labor cost):	1,486.40 Baht per day	1,486.40	Health Intervention and technology Assessment Program, 2010: online

4.4.2 Factors affect to the quantities of health care resources used

Treatments	Median (days)	Min-Max (days)	Source
▪ **Ceftazidime**			
▪ Duration of treatment with Ceftazidime in non-melioidosis	3	2-4	Wuthiekanun et l.(2005)
▪ Death within 48 hours after treated with Ceftazidime	2	1-2	Assumed all patients died on second day of treatment
▪ Ceftazidime treatment failure and died o Factored with probability of switch to Meropenem(0.516, SD= 0.09) o Treated with Ceftazidime 10 days o Treat with Ceftazidime/ Meropenem for another 13 days	23	14-29	Simpson et al. (1999)
▪ Ceftazidime treatment failure and survive o Factored with probability of switch drug (0.516, SD= 0.09) o Treated with Ceftazidime 10 days o Treat with Ceftazidime/ Meropenem for another 13 days	23	14-29	Simpson et al. (1999)
▪ Ceftazidime successfully treat	15	2-47	Simpson et al. (1999)
▪ **Meropenem**			
▪ Duration of treatment with Ceftazidime in non-melioidosis	3	2-4	Wuthiekanun et l.(2005)
▪ Death within 48 hours after treated with Meropenem	2	1-2	Assumed all patients died on second day of treatment
▪ Meropenem treatement failure and died o Factored with probability of switch drug (0.714, SD= 0.121) o Treated with Meropenem 23 days	23	14-29	Simpson et al. (1999)
▪ Meropenem treatement failure and survive o Factored with probability of switch drug (0.714, SD= 0.121) o Treated with Meropenem 23 days	23	14-29	Simpson et al. (1999)
▪ Ceftazidime successfully treat	14	5-43	Simpson et al. (1999)

4.4.3 Total cost:

Total cost calculated in this study is limited to cost of hospitalization and cost of drugs.

Sub-groups in decision analytic model:	Ceftazidime (Baht)	Meropenem (Baht)
▪ Treatment in non-melioidosis	464	12,907
▪ Death within 48 hours	309	8,605
▪ Treatment failure and died	65,569	133,143
▪ Treatment failure and survive	65,569	133,143
▪ Successfully treat without treatment failure	24,617	81,403

4.4.4 Outcomes

The RCT outcomes is hospitalization mortality. To make this cost-effectiveness analysis results comparable to other CEAs carried out in the Thai context and to the standard decision threshold used in economic evaluations in Thailand the number of lives saved is converted to "life year saved".

The average age of patients at the base case is 51 years, and according to WHO Life table (2008) the expectation of life at age 50 is 23.8 years. Therefore we will approximate that if the patient survives from severe meliodosis at age 51 s/he could expect to live for another 23 years or 16.44 years after discouting at a rate of 3% using the following formula:

$$\text{Discounted Life Year Saved} = \frac{vLY*(1-(1+r)^{-LE}}{r}$$

Where; vLY = value of each life year, rate=discount rate, LE = life expectancy

In addition, the WHO uses 1-3 times GDP per capita as a threshold to consider that health an intervention is cost effective (WHO-CHOICE 2005; HITAP 2007). 100,000 Baht is equivalent to approximately 1 GDP per capital and is the conventional threshold for Thai population used in cost-effectiveness evaluation.

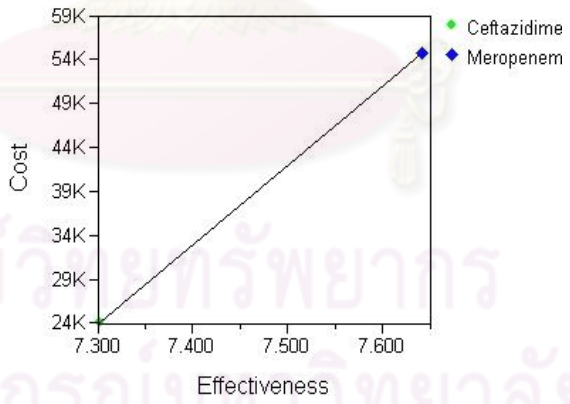
4.5 Cost-Effectiveness Analysis

The cost effectiveness analysis was taken in health care provider's perspectives. Meropenem and Ceftazidime were compared for costs and outcomes - summarized as the cost per life year saved. Using parameters solely extracted from the randomised controlled trial (Simpson et al., 1999). The analysis is done by using the TreeAge software version 2009. The result of analysis is illustrated in the table below.

Parenteral antibiotics	Expected Cost (Baht)	Incremental cost; I/C (Baht)	Expected Effectiveness (Life Year Saved; LYS)	Incremental effectiveness; I/E	Cost/ Effectiveness; C/E	Incremental cost effectiveness; ICER
Ceftazidime	24,015	-	7.302	-	3,289	-
Meropenem	54,726	+30,711	7.642	+ 0.34	7,162	90,338

The incremental cost is for treatment with Meropenem instead of Ceftazidime is 30,711 Baht (Figure 4.2). Meropenem increases life years by 0.34 year compared to Ceftazidime. In other words, for the cohort of 100 severe melioidosis patients to treat, Meropenem can save 34 additional years of life compared with treatment with Ceftazidime.

Figure 4.2 Cost-effectiveness Meropenem vs Ceftazidime



The incremental cost effectiveness ratio (ICER) can be derived as in the following calculation:

$$ICER = \frac{\text{Cost}_{\text{Meropemen}} - \text{Cost}_{\text{Ceftazidime}}}{\text{Effectiveness}_{\text{Meropemen}} - \text{Effectiveness}_{\text{Ceftazidime}}}$$

$$ICER = \frac{54{,}726 - 24{,}015}{7.642 - 7.302} = 90{,}338 \text{ Baht per one additional life year saved}$$

Meropenem is not a dominant choice of treatment because it provides higher effectiveness but with higher cost of treatment and the incremental cost effectiveness is 90,338 Baht per life year saved. The analysis so far using the baseline estimates suggests that Meropenem is cost-effective as the ICER is lower than the WTP threshold of 100,000Baht. There is however extensive uncertainty that requires sensitivity analyses to test the robustness of this result.

4.6 Sensitivity analysis

Sensitivity analysis will be done with 2 different approaches. First is one way sensitivity analysis applied to four different scenarios which will vary one of interested parameter at a time. Second approach is probabilistic sensitivity analysis (PSA) to vary all parameters at the same time to check how parameters uncertainties affect the analysis result, and to assess the probability that each treatment is cost-effective, given the uncertainty in all parameters simultaneously.

4.6.1 One way sensitivity analysis

a) Scenario of changes in probability of death after treatment failure in Meropenem group

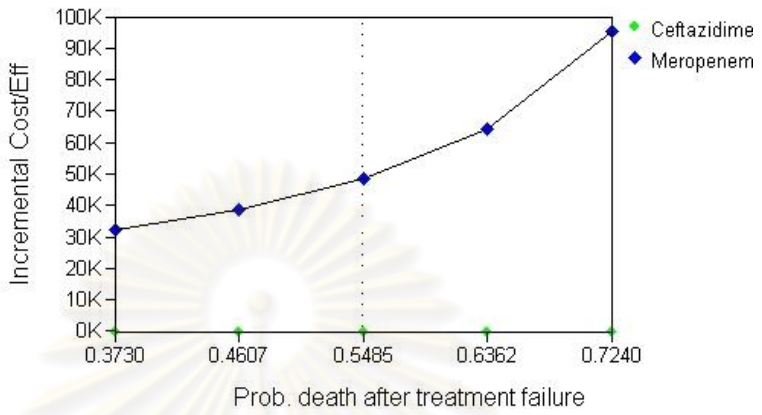
In the reference RCT, patients who had treatment failure in the imipenem group were later treated with Ceftazidime. The survival probability after treatment failure was therefore compromised by the lower effectiveness of Ceftazidime. It was clearly reported in the paper that imipenem showed a higher success rate in saving patients' lives who initially had Ceftazidime treatment failure, with a success rate of 64.7%. This is compared with a success rate of 23% in patients who initially had treatment failure with imipenem and were then switched to Ceftazidime (Simpson et al., 1999).

Therefore, the probabilities of death after treatment failure in Meropenem arm will be reduced from 71.4% to 54.9% which is the rate in Ceftazidime arm. The following are results:

Prob. Confirmed Melioidosis	Treatment	Cost	I/C	Effectiveness	I/E	C/E	ICER
0.373	Ceftazidime	24,016		7.3		3,289	
	Meropenem	54,727	30,711	8.25	0.95	6,634	32,398
0.461	Ceftazidime	24,016		7.3		3,289	
	Meropenem	54,727	30,711	8.09	0.79	6,762	38,802
0.549	Ceftazidime	24,016		7.3		3,289	
	Meropenem	54,727	30,711	7.94	0.64	6,895	48,362*
0.636	Ceftazidime	24,016		7.3		3,289	
	Meropenem	54,727	30,711	7.78	0.48	7,034	64,171
0.724	Ceftazidime	24,016		7.3		3,289	
	Meropenem	54,727	30,711	7.62	0.32	7,178	95,338

Decreasing of probability of treatment failure &death in the Meropenem arm has an inverse effect on the expected incremental effectiveness of Meropenem and subsequently decreasing the incremental cost effectiveness. With 16.5% of probability of death in treatment failure lowered, the incremental cost effectiveness reduced by 46% from 90,338 Baht to 48,362 Baht and almost doubled the incremental life years saved from 0.34 year to 0.64 year. In other words, the probability of Meropenem to be more cost-effectiveness is increasing as death rate in treatment failure reduces. Figure 4.3 below shows that the uncertainties in death rate after treatment failure of Meropenem is quite sensitive which can highly affect the incremental cost effectiveness and analysis result.

Figure 4.3 Changes in incremental cost-effectiveness when probability of death after treatment failure in Meropenem group reduced from 71.4% to 54.9%.



b) Scenario of decrease of incidence of confirmed melioidosis infection

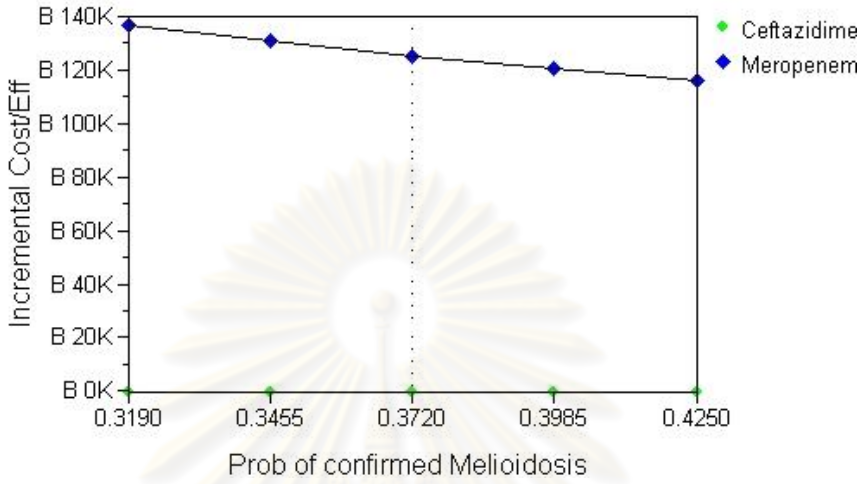
The incidence of confirmed melioidosis cased in the reference trial is suspected to be higher than in the real disease management setting because the patients were carefully screened into the trial with premeditated inclusion and exclusion criteria in order to enhance the chance of enrolling severe melioidosis patients. In this second scenario for the sensitivity analysis a lower probability of confirmed melioidosis cases is used, to reflect real clinical settings where the decision to treat is based only on clinical signs, symptoms and medical history which are often similar to other community acquired infection. Limmathurotsakul et al.(2010) reported that the overall incidence of confirmed melioidosis in Sapprasithiprasong hospital is about 37% (119 of 320) of suspected melioidosis cases. Therefore, this one way sensitivity analysis will be done by varying the probability of confirmed melioidosis in blood culture within 95% CI of 37%.

Results are as follows:

Prob. Confirmed Melioidosis	Treatment	Cost	I/C	Effectiveness	I/E	C/E	ICER
0.319	Ceftazidime	10,855		3.22		3,370	
	Meropenem	31,359	20,503	3.37	0.15	9,301	136,692
0.346	Ceftazidime	11,719		3.49		3,359	
	Meropenem	32,891	21,173	3.65	0.16	9,007	130,330
0.372	Ceftazidime	12,582		3.76		3,349	
	Meropenem	34,424	21,842	3.93	0.17	8,755	124,873*
0.399	Ceftazidime	13,445		4.02		3,341	
	Meropenem	35,957	22,512	4.21	0.19	8,537	120,143
0.425	Ceftazidime	14,308		4.29		3,334	
	Meropenem	37,490	23,182	4.49	0.2	8,346	116,002

When the incidence of melioidosis infection is reduced from 72% of suspected cases to 37% this increases the incremental cost-effectiveness, adding another 34,535 Baht (27.6%) to an additional life year saved in Meropenem group. This also reduced half the incremental effectiveness from 0.34 to 0.17 live year saved. Figure 4.4 below shows the ICER gradually decreasing as the probability of confirmed melioidosis increases; the interpretation is that a higher incidence yields a higher chance of Meropenem to be more cost-effectiveness.

Figure 4.4 Changes in incremental cost-effectiveness when probability of melioidosis confirmed patients in suspected infection patients



c) Scenario of death rate within 48 hours of Meropenem are equal to Ceftazidime

From the expert review survey, one of the four contacted experts responded with the recommendation to reduce the mortality rate of early death within 48 hours and death rate after treatment failure in Meropenem arm to be as low as Ceftazidime, because from his clinical experience Meropenem usually saves more lives. Thus a value of 20.6% was also used in the mortality rate of early death in the Meropenem arm. The result of varying probability of early death within 95% CI range of 20.6% is below.

Prob. death within 48h	Treatment	Cost	I/C	Effectiveness	I/E	C/E	ICER
0.130	Ceftazidime	24,016		7.3		3,289	
	Meropenem	61,915	37,900	8.86	1.56	6,985	24,254
0.169	Ceftazidime	24,016		7.3		3,289	
	Meropenem	59,594	35,578	8.47	1.17	7,036	30,466
0.208	Ceftazidime	24,016		7.3		3,289	
	Meropenem	57,273	33,257	8.07	0.77	7,093	43,024*
0.246	Ceftazidime	24,016		7.3		3,289	
	Meropenem	54,951	30,936	7.68	0.38	7,155	81,805
0.285	Ceftazidime	24,016		7.3		3,289	
	Meropenem	52,630		7.28		7,224	(Dominated)

Reducing the death rate within 48 hours has increased the incremental effectiveness of Meropenem arm from 0.34 to 0.77 life year saved and the incremental cost were reduced by half (from 90,338 to 43,024 Baht). In contrast, if the true death in 48 hours for Meropenem is higher or equal to 28.5%, Meropenem will be considered inferior to Ceftazidime (figure 4.5-a).

Figure 4.5: IE and ICER in relation to changes in probability of death within 48 hours

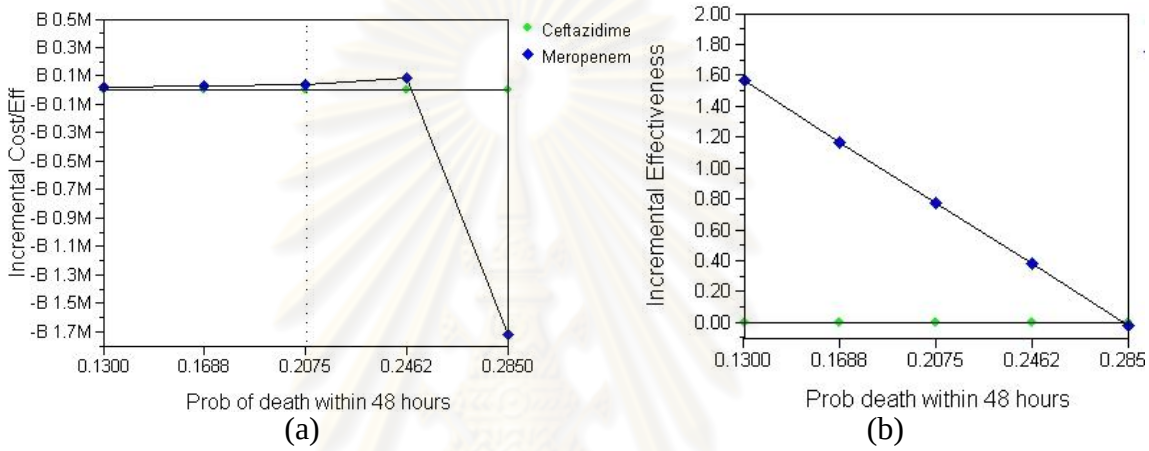
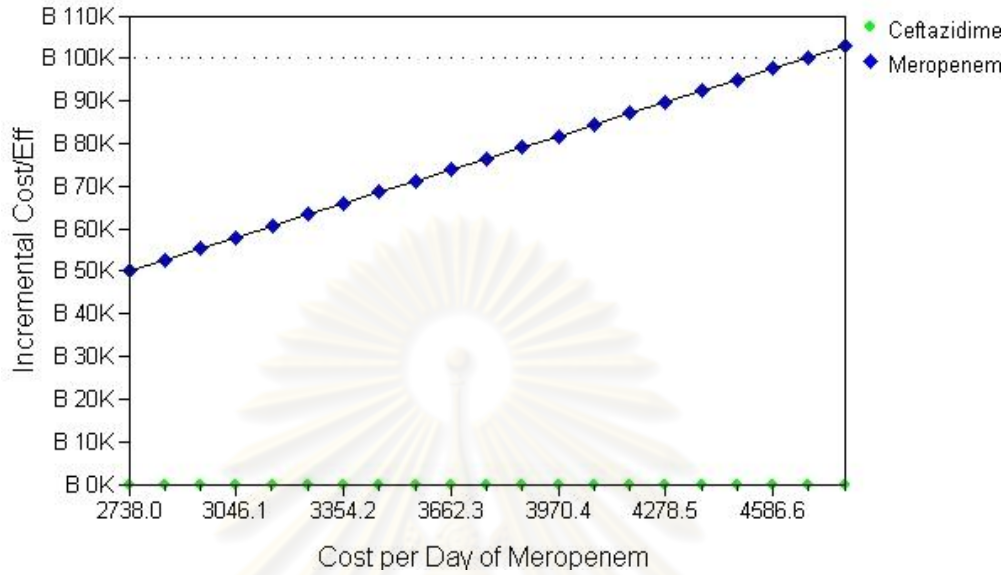


Figure 4.5-b shows the inverse linear relationship between incremental effectiveness of Meropenem and probability of early death, within a range of 13% to 28.5%. Across this range the effectiveness of Meropenem varies from being three times the number of life years saved to being less effective than Ceftazidime.

d) Scenario of reducing Meropenem drug cost

Meropenem is very expensive, with a cost fifty times higher than Ceftazidime. Therefore, this sensitivity analysis considers the price at which Meropenem would be more cost-effective than Ceftazidime. Cost of Meropenem incur to the hospital is 36% higher than the controlled cost announce in DMSIC; 1,434 Baht versus 912 Baht per gram. Therefore in this scenario drug cost will be reduced to DMSIC's price as a minimum and range up to +75%. The result of one way sensitivity analysis is shown in figure 4.6.

Figure 4.6 ICER and Meropenem cost ranged up to 75% of DMSIC price



If hold all other factors constant, as expected the incremental cost-effectiveness proportionally decreased with price, the incremental cost per one additional life year saved reduced from 90,338 Baht to 50,069 Baht. In the opposite, if the price is more than 4,600 Baht per day (1,533 Baht per gram), ICER will exceed WTP threshold.

4.6.2 Probabilistic Sensitivity Analysis

Many of the parameters obtained and used in this model are surrounded by extensive uncertainty and in many instances did not attain statistical significance using classical statistical tests, as reported in the original paper. . Therefore to check the robustness of analysis result and how parameter uncertainties affect the result, these were evaluated using a probabilistic sensitivity analysis (PSA).

Table 4.6 summarizes parameters and their assigned distribution used in PSA. Probabilities parameter are assigned a beta distribution as the value are contained between 0 and 1. The beta distribution parameters were calculated using the mean and standard deviation of the proportions reported in the RCT. For the length of stay and duration of drug administration parameters, information from the reference paper were lacking data for CI and standard deviation. Instead, a range of +/- 30% were adopted to use in PSA.

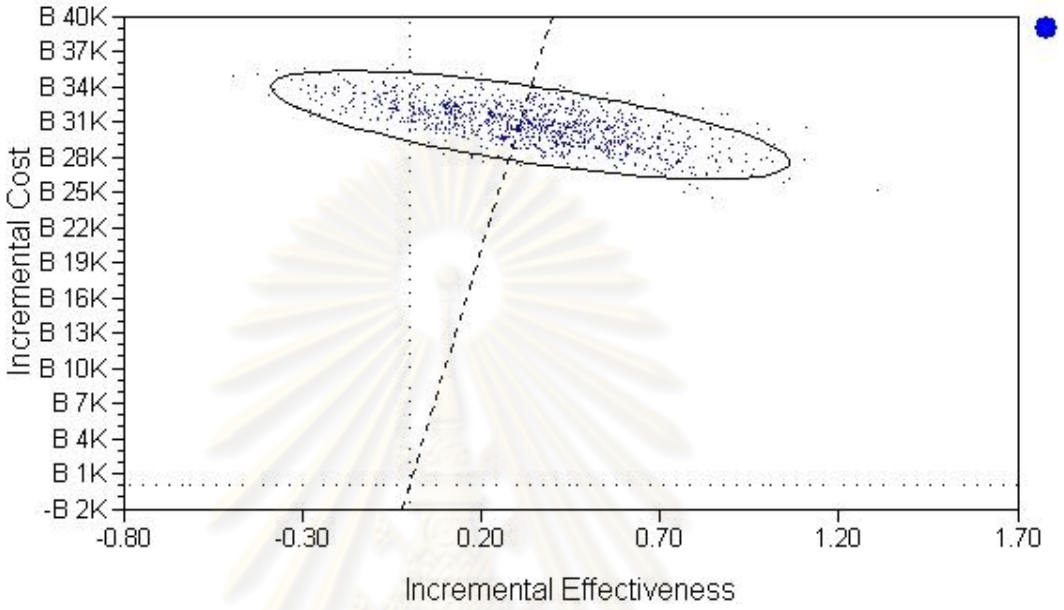
Table 4.6 Parameters estimates used in probabilistic sensitivity analysis

Parameter	Distribution		Distribution parameters
1)Probabilities parameters			
○ Patients with confirmed melioidosis infection	Beta	Mean = 0.723	SE*: 0.026
○ Death within 48 hours on Ceftazidime	Beta	Mean = 0.206	SE: 0.039
○ Treatment Failure on Ceftazidime	Beta	Mean = 0.413	SE: 0.057
○ Treatment Failure and died on Ceftazidime	Beta	Mean = 0.548	SE: 0.089
○ Death within 48 hours on Meropenem	Beta	Mean = 0.250	SE: 0.042
○ Treatment Failure on Meropenem	Beta	Mean = 0.203	SE: 0.048
○ Treatment Failure and died on Ceftazidime	Beta	Mean = 0.714	SE: 0.121
2) Cost parameters			
○ Hospitalization	Range+/- 30%	1418.40	1040.48 - 1932.32
○ Drug cost per day: Ceftazidime	Range+/- 30%	154.74	108.32 - 201.16
○ Drug cost per day: Meropenem	Range+/- 30%	4302.42	3011.70 - 5593.15

**SD* standard deviation

Using the above parameter values and assigned distributions, the PSA was done using a Monte Carlo simulation. This was done by randomly selecting values of each parameter in the model and recalculating the incremental cost effectiveness 10,000 iterations, then plotting the estimates on the incremental cost-effectiveness plane (figure 4.7). This illustrated the differences in the distributions of costs and effects of Meropenem and Ceftazidime.

Figure 4.7: Scatter plot of estimates incremental cost-effectiveness



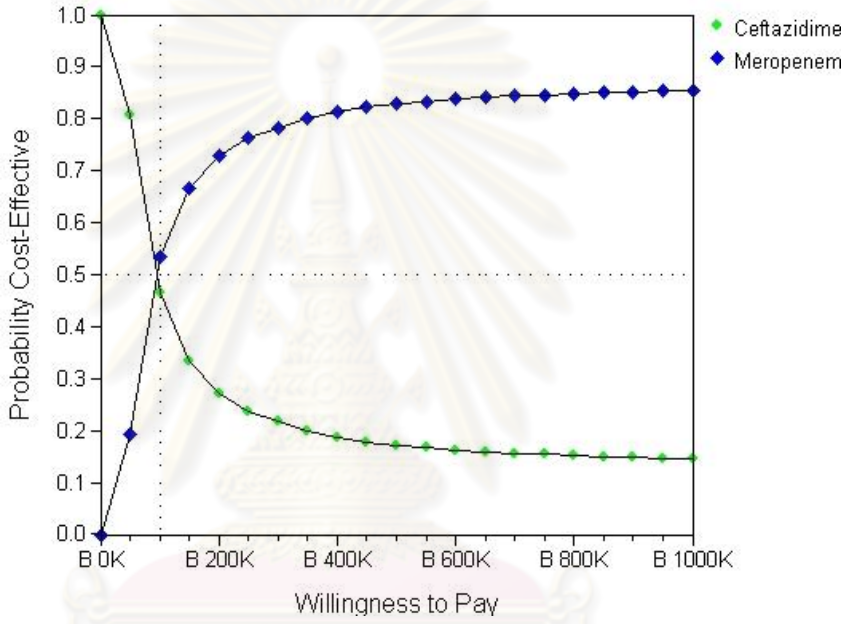
The graph shows that 87.40% of iterations the result was in quadrant 1, indicating that Meropenem had higher health gains and higher costs. The remaining 12.60% of the estimates fell in the inferior quadrant 2, implying that Meropenem was less effective and more costly.

The scatter plot also shows the assumed Willingness To Pay threshold of 100,000 Baht per life-year saved. Half of estimates (53.88%) are located below the WTP line and 46% are above (including the 12.60% of estimates in the inferior quadrant). The PSA therefore suggests that given the high uncertainty in many input parameters, there is a high probability of Meropenem not being cost effective.

4.7 Acceptability Curve

The cost-effectiveness aceptability curve describes the probability of each arm being preferred at different WTP thresholds. At a WTP of 100,000 Baht, the probability of Meropenem being the preferred option is over 53%, as was evident in Figure 4.8. At the higher WTP threshold of 300,000Baht, this probability increases to 80%.

Figure 4.8 Acceptability curve



CHAPTER V
DICUSSIONS AND CONCLUSIONS

5.1 Discussion

Melioidosis is one of the leading causes of death amongst infectious diseases in northeast Thailand therefore it is crucial that it is treated with the most effective and cost-effective treatment. Ceftazidime has been shown to be more effective than previous drugs, however it is being investigated whether Meropenem is a better alternative. The only randomised controlled trial comparing effectiveness between Meropenem and Ceftazidime is still ongoing and the trial result may be available in the next couple years. Clinicians and microbiologists have a strong belief that Meropenem can reduce overall mortality rate and lower treatment failure rate and save more lives from treatment failure than other drugs. This preliminary cost-effectiveness analysis of two melioidosis drugs was performed with best available evidences. The baseline result from this analysis suggests that Meropenem can be a cost effective alternative to Ceftazidime. The results however are very sensitive to the uncertainties in parameter estimates therefore there is much room for improvement in future studies to be able to present more robust results. The following are what have been learned and to be discussed.

4.6.3 Uncertainties in the Baseline Parameters

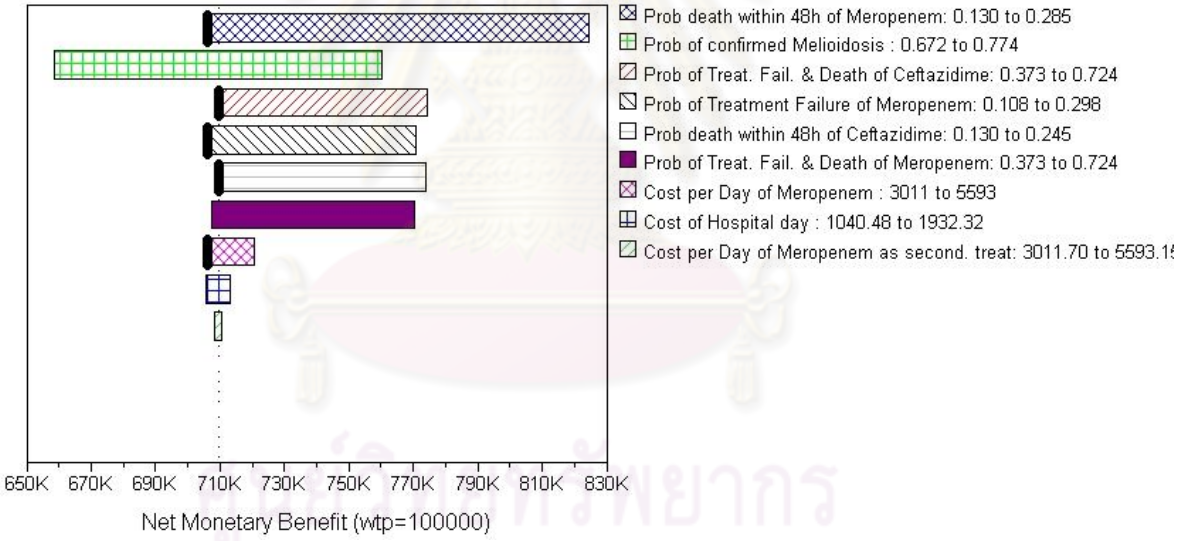
In this modeling-based economic evaluation, baseline parameters used are from one randomised controlled trial conducted by Simpson et al (1999). Using information from a randomized clinical trial helps avoid the selection bias that occurs in observational studies in real setting, where Meropenem is primarily used for more severe cases. Using the base case results as point estimates, Meropenem appears to be cost-effectiveness.

However, in the trial some of the differences between the drugs were not statistically significant such as overall mortality rate in the two groups were 36% versus 38% in imipenem and Ceftazidime. Instead of rejecting this result because the trial result was below the arbitrary p-value, the PSA (Probabilistic Sensitivity Analysis) allows us to use these estimates in a way that captures the uncertainty surrounding these parameters in the

model. The sensitivity analysis shows that despite this uncertainty and the uncertainty surrounding other key parameters there is a high probability of Meropenem being cost effective, particularly at the higher WTP threshold of 300,000 Baht, where there is a probability of over 80% that Meropenem is cost-effective.

The one way sensitivity analysis scenarios evidenced that study results are highly sensitive to a few parameters; probability of early death (within 48 hours), probability of death after treatment failure, incidence of melioidosis infection. The following tornado diagram is a set of one-way sensitivity analyses which illustrates the rank of which parameters were surrounded by uncertainty that was most influential on the analysis' results.

Figure 5.1 Tornado Diagram of Cost-Effectiveness Analysis



Each horizontal bar of the diagram represents the range of possible outcomes caused from changes in each parameter, across a plausible range. In summary, the analysis results are most influenced by the probability of death within 48 hours of Meropenem and probability of incidence of melioidosis. These are both parameters for which data are currently being collected in clinical and observational studies which could serve to make the results far more robust.

4.6.4 The drug cost

The drug cost is an obvious factor to determine if Meropenem can be not only more effective but also more cost-effective than Ceftazidime. Drug costs to the hospital are subjected to the purchasing power of the hospital, where larger amounts purchased by larger hospitals can lower the cost. The current purchasing price at Sapprasithiprasong hospital is 1434 Baht per gram (in 2011 Baht). The one way sensitivity analysis suggested that if the price increased to more than 1,533 Baht per gram, the ICER will exceed the WTP threshold and Meropenem would not be considered cost-effective.

DMISC has been trying to control the drug price by giving the reference price to all public hospitals and health care facilities. There are also unofficial reports that the Thai Government Pharmaceutical Organization plans to locally produce Meropenem, this could encourage clinicians to prescribe Meropenem to treat melioidosis patients more frequently. As demand for the drug increases, the short run result could be larger purchasing volume and the price incurs to hospital will be lower. In the long run, with higher demand it is possible that the cost of producing Meropenem will be reduced and the lower price can be sustained.

4.6.5 Lower mortality rate in better supportive care

There are differences in mortality rates reported in different settings. The rate in Darwin Royal hospital, Australia (approximately 20%) and Srinakarin hospital (approximately 10%) are much lower compared to Sapprasitprasong hospital (average 42%) in Ubon Rachthani. Possible underlying reasons for this is because of the available intensive care facilities. Almost half of severe melioidosis patients presented with septicemia, the treatment under intensive care unit yield better chances to survive. The possible lower mortality rate with better supportive care is considered to be similar in both drugs therefore the incremental cost effectiveness is expected not to be different from this analysis result.

4.6.6 Limitations

- **Use of Imipenem effectiveness**

  With the limited of Meropenem's effectiveness information, Imipenem's was used in this analysis. Although robustness of the result was tested by probabilistic sensitivity analysis, but all parameters still contain major underlying uncertainties which inevitably affect to the reliability of the analysis result. However as we took the conservative perspective, this analysis results allow us to identify of which situation that Meropenem might be more or less cost-effective than Ceftazidime.

- **Analysis outcomes**

  The outcome of this analysis is measured in term of life years saved to make this cost-effectiveness analysis results comparable to other economic evaluations carried out in Thailand and to the standard decision threshold of 100,000 Baht. However, this decision threshold is normally applied with Quality Adjusted Life Years (QALYs). Because quality of life values for severe and recovered melioidosis patient are not yet available this was not accounted for in the analysis. As a result, use of life years instead of QALYs can over-estimate the cost-effectiveness of the results, particularly if the quality of life of the patients is low after surviving treatment.

- **Underestimating Cost**

  This evaluation has taken health care provider' perspective that includes costs incurred from direct medical resource consumption. In this analysis, only hospitalization cost and cost of drugs were included but other costs such as diagnostics and other treatments given during inpatient stay were excluded. And the unit costs used were not direct cost from Sapprasithprasong hospital but adopted from Riewpaiboon and HITAP (2009).

The total cost was mainly driven by the length of stay. The reference paper only reported overall length of stay of patients with and without treatment failure cases but these were not identified specifically in each arm. Hence the same length of stay was inputted into both groups of treatment, with the difference between the arms resulting only from the proportion in whom treatment fails.

The total cost in this analysis therefore is not a precise representation of the true cost of each treatment and tend to be underestimated. For preliminary research purpose as a foundation for future research, this cost is sufficient to assess the cost differences and to allow this cost-effectiveness analysis to determine if Meropenem can be superior to Ceftazidime.

- **The model**

  The structure of the decision model can be improved by adding branches to demonstrate the chance of switching therapy and subsequent probability of death. The model could also factor in co-morbidities such as diabetes, renal failure, splenic or liver abscesses as in some of these sub-groups the cost-effectiveness could be different as these require different additional procedures, respond to treatment differently and incur different costs.

  The model assessed outcomes only in the primary admission, although the RCT reported that patients in Ceftazidime arm had a higher probability of being readmitted. The numbers however were very low therefore it was decided to exclude this. If it were included it would strengthen the cost-effectiveness of Meropenem.

5.2 Recommendations for further analyses

- **Use of QALYs as outcomes**

  Future analyses should use differences in quality adjusted life years (QALYs) as a consequence of the interventions. The utility survey of this disease should be done in the future. With the availability of utility score, the study result can be truly comparable to national threshold and other interventions conduct in the country.

- **The use of Markov Models**

  A Markov model is a possible choice for a future study use to represent the course of disease management. According to the natural course of diseases, severe melioidosis patients admissions will often enter critical condition and are very slow to respond to treatment, therefore in one hospitalization a patient may have a transition period between being treated in the intensive care unit, incurring much higher costs, and the general wards. Markov models allow these interchange transitions in different medical wards to be included in the model and captured in the cost-effectiveness analysis.

- **Expected Value of Perfection Information (EVPI)**

  The result of economic evaluation is often used to determine which treatment should or should not to be opted and funded. As was shown in this analysis, even where the baseline estimate suggests that an intervention is cost-effective there can still be a high probability of this result being wrong. By evaluating the uncertainty in the analysis, it is possible to estimate the value of reducing this uncertainty through further research.

  The expected value of perfect information (EVPI) is determined by the difference of the expected value with perfect information and the expected value with current information and then shows the maximum amount policy makers should be willing to pay to eliminate uncertainty by investing in further research.

5.3 Conclusions

Using the point estimates from the base case, the incremental cost for treatment with Meropenem is 31,000 Baht and the incremental effectiveness is 0.34 life years saved, the additional cost for one life year saved is about 90,000 Baht, which is below the WTP threshold of 100,000 Baht indicating that Meropenem is cost-effective. After taking all uncertainties into account in the Monte Carlo simulation, 87% of 10,000 estimates are in quadrant 1 of incremental the cost-effectiveness plane and 54% of estimates are below the WTP threshold; therefore the evidence in favour of the cost-effectiveness of Meropenem is not yet compelling.

Sensitivity analyses showed that death rate within 48 hours, rate of treatment failure and death after the failure play important role in result's robustness. The highest impact parameter is the death rate within 48 hours of treatment with Meropenem, currently set at 25%. If the value is equal or higher than 28.5%, Meropenem will turn out to be inferior to Ceftazidime. In another word, Meropenem can be a favorable choice of treatment when it can save at least 75 out of 100 patients from early death (within 48 hours). If less than 71 patients survived from this critical period, Meropenem is not a cost-effective choice anymore.

The decision on whether to adopt meropenem will depend on how risk averse the decision makers are. If policy makers are risk-neutral they might conclude that as the probability of meropenem being cost-effective is over 50% it should be adopted. There is however clearly a need for better information of critical parameters. Therefore, it is inconclusive that Meropenem should be adopted to replace the standard treatment from this analysis. This analysis will be repeated when the current ongoing trial comparing Meropenem and Ceftazidime is completed to advise policy makers on how best to treat severe melioidosis.

REFERENCES

Barton, GR., Briggs, AH., and Fenwick, E. (2008) Optimal Cost-Effectiveness Decisions:The Role of the Cost-Effectiveness Acceptability Curve (CEAC), the Cost- Effectiveness Acceptability Frontier (CEAF), and the Expected Value of Perfection Information (EVPI). *International Society for Pharmacoeconomics and Outcomes Research (ISPOR),* 11(5), 886–897.

Buchanan, J., Mihaylova, B., Gray, A., and White, N. (2010) Cost-Effectiveness of Pre-Referral Antimalarial, Antibacterial, and Combined Rectal Formulations for Severe Febrile Illness. *PLoS ONE,* 5(12), e14446. doi:10.1371/journal.pone.0014446

Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health. Annual Epidemiological Surveillance Report 2007, pp. 53-55. Retrived from http://www.boe.moph.go.th/.

Chaowagul, W., Suputtamongkol, Y., Dance, DA., Rajchanuvong, A., Pattara-arechachai, J., and White, NJ. (1993). Relapse in melioidosis: incidence and risk factors. *Journal of Infectious Diseases*; 168, 1181–1185.

Chaowagul, W., et al. (1989). Melioidosis: a major cause of community-acquired septicemia in northeastern Thailand. *J Infect Dis*, 159, 890-9.

Cheng, AC., and Currie, BJ. (2005). Melioidosis: Epidemiology, Pathophysiology, and Management Clinical *Microbiology Reviews*, 383–416.

Cheng, AC., Fisher, DA., Anstey, NM., Stephens, DP., Jacups, SP., and Currie , BJ. (2004). Outcomes of patients with melioidosis treated with Meropenem. *Journal of Antimicrobial Chemotherapy*, 48,1763–1765.

Cheng, AC., West, TE., Limmathurotsakul, D., and Peacock, SJ. (2008) Strategies to reduce mortality from bacterial sepsis in adults in developing countries. *PLoS Medicine,* 5(8), e175. doi:10.1371/journal.pmed.0050175

Cheng, AC., et al. (2006). Prospective evaluation of a rapid immunochromogenic cassette test for the diagnosis of melioidosis in northeast Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 100(1):64-7.

Drummond, M. and McGuire, A. (2007). *Economic Evaluation in Health Care: Merging Theory with Practice.* Oxford: Oxford Medical Publications.

Drummond, MF., Sculpher, MJ., Torrance, GW., O'Brien, BJ., and Stoddart, JL. (2005). *Methods for the Economic Evaluation of Health Care Programmes*. *Third Edition*. Oxford: Oxford Medical Publications.

Edwards, SJ., Wordsworth, S., and Clarke, MJ. (2011). Treating pneumonia in critical care in the United Kingdom following failure of initial antibiotic: a cost-utility analysis comparing Meropenem with piperacillin/tazobactam. *The European Journal of Health Economics*. DOI 10.1007/s10198-011-0296-0.

Edwards, SJ., Campbell, HE., and Plumb, JM. (2006). Cost-utility analysis comparing Meropenem with imipenem plus cilastatin in the treatment of severe in fections in intensive care. *The European Journal of Health Economics,*7:72–78 DOI 10.1007/s10198-005-0333-y

Estes, DM., Dow, SW., Schweizer, HP., and Torres, AG. (2010). Present and future therapeutic strategies for melioidosis and glanders. *Expert Review of Anti-Infective Therapy,*8(3): 325–338. doi:10.1586/eri.10.4.

Koh, G.C.K.W., et al. (2011). Glyburide Is Anti-inflammatory and Associated with Reduced Mortality in Melioidosi. *Clinical Infectious Diseases,* 1–9. DOI: 10.1093/cid/ciq192

Health Technology Assessment Guideline 2008. Journal of the Medical Association of Thailand, 91 (2). Retrived from http://www.ispor.org/.

Inglis, TJJ. (2010). The Treatment of Melioidosis. *Pharmaceuticals*, 3, 1296-1303. doi:10.3390/ph3051296

Leelarasamee, A., Sathirakul, K., Trakulsomboon, S., Pongpech, P., and Naenna, P. (2008) Bioequivalence Study with Comparative Antibacterial Activity of a Generic Meropenem. *Journal of Infectious Diseases and Antimicrobial Agents*, 25(2), 63-72.

Limmathurotsakul, D., Chaowagul, W., Day, N.P.J., and Peacock, S.J. (2009). Short Report: Patterns of Organ Involvement in Recurrent Melioidosis. *American Journal of Tropical Medicine and Hygiene,* 81(2), 335–337.

Limmathurotsakul, D., et al. (2010). Increasing Incidence of Human Melioidosis in Northeast Thailand. *American Journal of Tropical Medicine and Hygiene*, 82(6), 1113–1117.

Limmathurotsakul, D., et al. (2010). Defining the true sensitivity of culture for the diagnosis of melioidosis using Bayesian latent class models. *PLoS One*, 30; 5(8):e12485.

Maude, R.R., et al. (2011) Prospective observational study of ultrasound to assess intraabdominal abscesses in Melioidosis in Northeast Thailand. The poster presented in Oxford Tropical Network Meeting, February 2011.

Morris, S., Devlin, N., and Parkin, D. (2007) *Economic Analysis in Health Care*. John Wiley & Sons, Ltd.

Smith, MD., Wuthiekanun, V., Walsh, AL., and White, NJ. (1994) Susceptibility of Pseudomonas pseudomallei to some newer beta- lactam antibiotics and antibiotic combinations using time-kill studies. *Journal of Antimicrobial Chemotherapy*, 33, 145-149.

Smith, MD., Wuthiekanun, V., Walsh, AL., and White, NJ. (1994). Susceptibility of *Pseudomonas pseudomallei* to some newer beta-lactam antibiotics and antibiotic combinations using time-kill studies. *Journal of Antimicrobial Chemotherapy*, 33, 145-149.

Talbird, SE., Brogan, AJ., Winiarski, AP., and Sander, B. (2009). Cost-effectiveness of treating influenzalike illness with oseltamivir in the United States. *American Journal of Health-System Pharmacy*, Vol 66.

Thamlikitkul, V., Tiengrim, S., Chalermsri, C., Chinsawangwatanakul, P., and Suddhichupaiboon, S. (2010) Microbiological equivalence of serum bacteriostatic and bactericidal activities of the sera from healthy volunteers receiving original Meropenem (Meronem®) and generic meropenem (Mero®). *Journal of The Medical Association of Thailand*; 93 (Suppl. 1): S110-116.

Westling, K. (2009) Cost-Effectiveness Analysis of Treatment of Methicillin-Resistant Staphylococcus aureus Bacteremia and Endocarditis Is a Dificult Issue. *Clinical Infectious Diseases*, 49, 699–701

White, NJ., Dance, DA., Chaowagul, W., Wattanagoon , Y., Wuthiekanun, V., and Pitakwatchara, N. (1989) Halving of mortality of severe melioidosis by Ceftazidime.*The Lancet*, 2, 697-701.

Wuthiekanun, V., et al. Rapid immunofluorescence microscopy for diagnosis of melioidosis.(2005). *Clinical and Diagnostic Laboratory Immunology*, 12(4): 555-6.

Pai, M., et al. (2004). Systematic reviews and meta-analyses: an illustrated, step-by-step guide. *The National Medical Journal of India*,17(2), 86-95.

Youngkong, S., Riewpaiboon, A., Towanabut, S. and Riewpaiboon, W. (2004). Unit Costs of Medical Services at Prasat Neurological Institute. *Srinakharinwirot University Journal of Pharmacy Science*, 9(1)

APPENDICES

Appendix A:

Systematic Review Sheet: Effectiveness of Ceftazidime and Meropenem in treatment of melioidosis **Sheet no_____**

Author, year	Study Type	Population & Sample size	Intervention	Outcomes (Risk Difference, Relative risk, Odd ratio, CI)	Note:

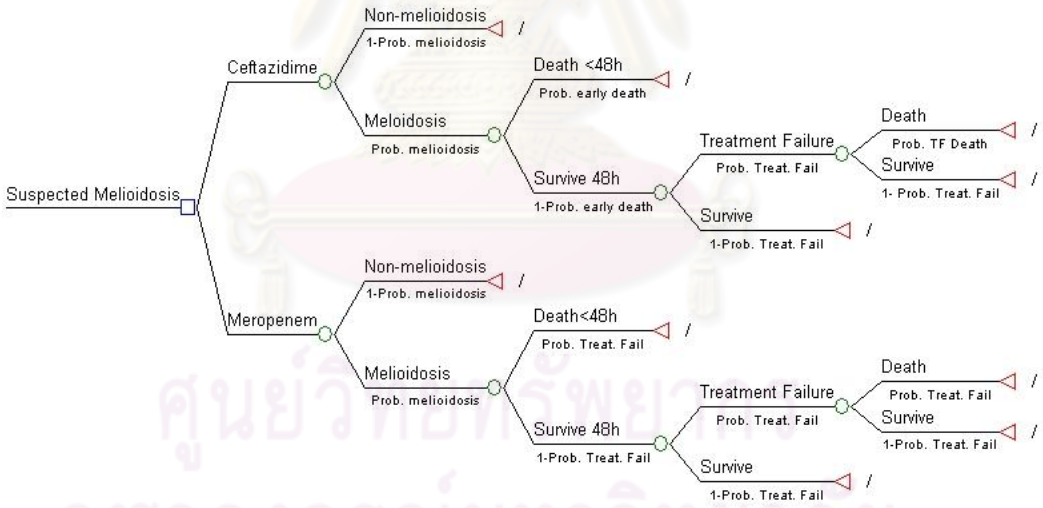
Appendix B:

Expert opinion sheet:

Thesis title: Economic Evaluation Of Ceftazidime And Meropenem For The Treatment Of Severe Melioidosis, Northeastern Region In Thailand

This study aims to determine the cost-effectiveness of cefazidime and Meropenem in treatment for severe melioidosis.

The course of severe melioidosis treatment and outcomes are drawn in the following decision tree. The probabilistic parameters used in the decision tree were obtained from randomised controlled trial compare between imipenem and ceftizidime conducted by Simpson et al in 1999. Because the Meropenem's effectivenss compared to Ceftazidime from RCT is not yet available therefore the imipenem which is the antibiotic in the carbarpenem group was adopted as a best evidence to represent Meropenem in this study.



Model assumptions:

1. All patients have been diagnosed severe melioidosis and are assumed to have the same conditions when Ceftazidime/ Meroenem administered. Although in current practice Meropenem will be used to treat more severe patient (severe melioidosis with more serious condition), but in this analysis would like to take conservative analysis approach to investigate cost-effectiveness of Meropenem compare to standard treatment. If the study result shows that Meropenem is more cost-effectiveness than

Ceftazidime thus it may be able to conclude that if Meropenem were given to the same condition will still yield the better cost-effectiveness result.

2. Patients' clinical sign and symptoms worsen and occurred after receiving IV treatment more than 72 hours e.g. development of shock or organ function failure (kidney or liver). Or the patient still has a high fever and the clinical conditions are not improving after 14 days of IV treatment. In this model all patients are assumed to have only one treatment failure. The treatment after treatment failure is:

- If the patient first received Ceftazidime will switch to Meropenem until discharged or die.
- If Meropenem treatment failure, patient will continually receive Meropenem until discharged or die.

The assumption made of drugs used after treatment failure is based upon the current practice and expert opinion.

3. The antibiotic resistant and adverse events that may occur from each drug are not taken into account in this model. This will be considered as a limitation of the model in this study.

4. All patients are assumed to stay in one ward until successfully treated and discharged or die.

5. In severe melioidosis patients often have 2 co-morbidity such as diabetes and renal impairment and are assumed to have no difference in mortality rate in the model. This is because there is limitation of report in mortality differences in patients who have co-morbidity and those who have not.

I would like to have your opinion regarding the probability in decision tree above, if they can represent Meropenem's effectiveness. If not, please suggest the probability is best representing Meropenem's effectiveness. Please fill in your opinion in below table. Your support is very much appreciated.

Probabilities	**Probability from published paper; Simpson et al. (1999)**	**Experts' opinion**
Probability of confirmed melioidosis infection in suspected patients	0.722 (72.2%)	☐ Agree ☐ Not agree; probability better represents confirmed among suspected melioidosis should be: |__|.|__| |__||__| or |__||__|.|__| |__|%

Ceftazidime treatment group:		
Death in 48 hours	0.206 (20.6%)	☐ Agree ☐ Not agree; probability better represents Meropenem should be: |__|.|__| |__||__| or |__||__|.|__| |__|%
Treatment failure *	0.413 (41.3%)	☐ Agree ☐ Not agree; probability better represents Meropenem should be: |__|.|__| |__||__| or |__||__|.|__| |__|%
Death after treatment failure	0.549 (54.9%)	☐ Agree ☐ Not agree; probability better represents Meropenem should be: |__|.|__| |__||__| or |__||__|.|__| |__|%
Imipenem (will represent Meropenem) treatment group:		
Death in 48 hours	0.250 (25%)	☐ Agree ☐ Not agree; probability better represents Meropenem should be: |__|.|__| |__||__| or |__||__|.|__| |__|%
Treatment failure *	0.200 (20%)	☐ Agree ☐ Not agree; probability better represents Meropenem should be: |__|.|__| |__||__| or |__||__|.|__| |__|%
Death after treatment failure	0.714 (71.4%)	☐ Agree ☐ Not agree; probability better represents Meropenem should be: |__|.|__| |__||__| or |__||__|.|__| |__|%

Appendix C:

Discarded resources consumption quantities from Sappasitprasong hospital (1997 - 2006)

Ceftazidime group:

The result of identifying melioidosis infections subgroup as according to the decision tree model:

Group	Frequency	Percent	Cumulative
Group 1	341	32.79	32.79
Group 2	612	58.85	97.63
Group 3	26	2.50	94.13
Group 4	61	5.87	100.00
Total	1,040	100	

Where group 1-4 were group of patient whom recieved Ceftazidime as a first treatment.

Group 1: Patients who died within 48 hours
Group 2: Patients who died after treatment failure
Group 3: Patients who survived after treatment failure
Group 4: Patients who survived without treatment failure

Carbapenem group:

Group 5-8 were group of patient whom recieved carbapenem antibiotics (Meropenem/ imipenem) as a first treatment.

Group 5: Patients who died within 48 hours
Group 6: Patients who died after treatment failure
Group 7: Patients who survived after treatment failure
Group 8: Patients who survived without treatment failure

Group	Frequency	Percent	Cumulative
Group 5	12	40.00	40.00
Group 6	5	16.67	56.67
Group 7	1	3.33	60.00
Group 8	12	40.00	100.00
Total	30	100	

Quantities of health care resources used in each treatment group

Group 1: Ceftazidime patients who died within 48 hours

Variables	Observations	Mean	Standard Deviation	Min.	Max.
Length of Stay	341	4.97	6.63	0	39
Ceftazidime duration	341	4.39	5.72	0	36
Carbaopenem duration	341	0	0	0	0
Hematology test	340	1.79	1.20	1	14
Biochemistry test	340	2.50	1.99	1	15
Serology test	49	1.06	0.31	1	3

Group 2: Ceftazidime patients who died after treatment failure

Variables	**Observations**	**Mean**	**Standard Deviation**	**Min.**	**Max.**
Length of Stay	612	14.75	10.11	1	110
Ceftazidime duration	612	13.57	7.95	0	93
Carbaopenem duration	612	0	0	0	0
Hematology test	605	1.79	1.20	1	14
Biochemistry test	578	2.51	1.81	1	13
Serology test	195	1.08	0.36	1	4

Group 3: Ceftazidime patients who survived after treatment failure

Variables	**Observations**	**Mean**	**Standard Deviation**	**Min.**	**Max.**
Length of Stay	26	19.46	16.20	0	64
Ceftazidime duration	26	12.07	12.74	1	64
Carbaopenem duration	26	6.76	7.43	1	28
Hematology test	26	3.65	2.84	1	12
Biochemistry test	26	6.23	5.36	1	23
Serology test	10	1	0	1	1

Group 4: Ceftazidime patients who survived without treatment failure

Variables	Observations	Mean	Standard Deviation	Min.	Max.
Length of Stay	61	34.11	15.37	5	93
Ceftazidime duration	61	16.11	11.13	1	56
Carbaopenem duration	61	14.63	8.64	1	39
Hematology test	61	3.47	2.10	1	11
Biochemistry test	61	5.36	3.577	1	21
Serology test	20	1.2	0.41	1	2

Group 5: Carbapenem patients who died within 48 hours

Variables	Observations	Mean	Standard Deviation	Min.	Max.
Length of Stay	12	7.16	4.82	1	13
Ceftazidime duration	12	0	0	0	0
Carbaopenem duration	12	3.83	3.95	1	12
Hematology test	12	2.25	1.81	1	6
Biochemistry test	12	3.33	2.38	1	8
Serology test	5	1	0	1	1

Group 6: Patients who died after treatment failure

Variables	Observations	Mean	Standard Deviation	Min.	Max.
Length of Stay	5	7.6	3.50	4	13
Ceftazidime duration	5	0	0	0	0
Carbaopenem duration	5	5.8	3.42	3	10
Hematology test	5	1	0	1	1
Biochemistry test	5	1.2	0.44	1	2
Serology test	2	1	0	1	1

Group 7: Patients who survived after treatment failure

Variables	Observations	Mean	Standard Deviation	Min.	Max.
Length of Stay	1	18	0	18	18
Ceftazidime duration	1	2	0	2	2
Carbaopenem duration	1	6	0	6	6
Hematology test	0	0	0	0	0
Biochemistry test	0	0	0	0	0
Serology test	0	0	0	0	0

Group 8: Patients who survived without treatment failure

Variables	Observations	Mean	Standard Deviation	Min.	Max.
Length of Stay	12	31.5	13.92	14	64
Ceftazidime duration	12	2.75	4.53	0	14
Carbaopenem duration	12	17.08	10.40	6	36
Hematology test	12	2.91	1.16	2	6
Biochemistry test	12	3.75	2.00	2	9
Serology test	5	1	0	1	1

BIOGRAPHY

Name: Viriya Hantrakun

Sex: Female

Date of Birth: 15 December 1975

Office Address: Mahidol Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Rd., Bangkok 10400, Thailand

Home Address: 8/173 The PlantCiti, Ladproa 71, Moo 4, Ladproa, Bangkok, 10230, Thailand

Tel: +66-81-4234811

E-mail address: viriya@tropmedres.ac

Nationality: Thai

Education: Master of Management, College of Management Mahidol University

Current position: Clinical Trial Administrative Assistant, MORU

Past Experience:

1. International Sales Manager, NanoAsia Co., Ltd.
2. Club Manager, Leaders Wellness Co., Ltd.