ECONOMIC EVALUATION IN INTENSIVE CARE: THE CASE OF SDD

A thesis submitted for the degree of Doctor of Philosophy

by

Rachel Elliott

Health Economics Research Group, Department of Economics,

Brunel University.

November 1995

ACKNOWLEDGEMENTS

I am grateful to the Office of the Chief Pharmacist, Department of Health for their financial support and the Pharmacy Practice Research Resource Centre for their administrative support.

I am particularly grateful to my supervisor, Professor Martin Buxton, for his help, expertise and advice throughout the course of the thesis.

In addition, I wish to thank everyone in the Health Economics Research Group, without whose help and forbearance this thesis would never have been completed. I am also grateful to those in the Economics Department at Brunel University for their help and advice in the statistical analysis. Professor Len Skerratt's support has been particularly helpful.

I would like to thank Dr Mark Palazzo, Mr Tony Pritchard, Ms Chris Shaw, Ms Maie Templeton and all the staff working on the intensive care unit at Charing Cross Hospital. I also wish to thank Dr Chris Dark, Dr Anne Knight and Dr Andrew Thorniley, Ms Sue McKie and all the staff working on the intensive care unit at Hillingdon Hospital. Without their co-operation this research project would not have been possible.

I would like to thank Professor Martin Cave and Professor Nick Barber for agreeing to examine this thesis and for their stimulating and pertinent thoughts, comments and suggestions during the *viva voce* examination.

Finally, I would like to thank all my work colleagues, friends and family for all their support, patience and encouragement.

This thesis is dedicated to my mother

ABSTRACT

The aim of this thesis was to examine the use of modelling techniques in the economic evaluation of *selective decontamination of the digestive tract* (SDD), used to prevent *intensive care unit* (ICU) acquired pneumonia. The need for evidence for the effectiveness and cost effectiveness of technologies used in intensive care was highlighted through an examination of the literature. The clinical and economic issues pertinent to ICU-acquired pneumonia and SDD were described. It was suggested that an economic evaluation of SDD was required. An evaluation using modelling techniques was proposed. A secondary economic evaluation of SDD was carried out, utilising a decision-analytic model and published clinical and economic evidence to derive cost/outcome ratios. This analysis showed that SDD could be a dominant therapy, but improved economic and long term outcome evidence was required to increase the robustness of conclusions. This thesis concentrated on improving the economic evidence. A national survey of SDD use provided information on clinical practice. A prospective observational study was carried out at two British ICUs to obtain evidence on the economic impact of ICU-acquired pneumonia. The impact of infection and confounding factors on resource use was handled quantitatively, using regression techniques. It was found that ICU-acquired pneumonia significantly increased length of ICU stay. These two sets of empirical data were used in a revised economic evaluation of SDD. SDD was found to be a dominant therapy at both centres. Uncertainty around cost/outcome ratios was considered to be decreased, or at least quantified, by this primary economic evidence. This thesis concludes that modelling has a place in economic evaluation in intensive care, if rigorous methods are used. It has also demonstrated that current, reliable and applicable economic evidence is a prerequisite to any economic evaluation, if it is to be included in the decision-making process.

CONTENTS *page*

Contents *page*

Contents *page*

Contents *page*

List of Tables

List of Figures

Figure *Page*

List of Appendices

GLOSSARY

Aspiration	Pathologic inhalation of vomitus or mucus into the respiratory tract which may occur when the patient is unconscious or anaesthetized.
Bacterial resistance to drugs	The ability of a microorganism to withstand effects of a drug that is lethal to most members of its species.
Blind antibacterial treatment	Use of antibiotics to treat an infection when there is no positive microbiological culture to direct therapy.
Gram-negative bacteria	Group of bacteria identified by a chemical stain test, often implicated in nosocomial infection. Members include *Pseudomonas aeruginosa* and *Escherichia coli*.
Gram-positive bacteria	Group of bacteria identified by a chemical stain test, often implicated in nosocomial infection. Members include *Staphylococcus aureus* and *Streptococcus faecalis*.
ICU-acquired pneumonia	Pneumonia that is not present or incubating on admission to ICU.
Early onset pneumonia	Pneumonia that becomes clinically evident within the first 48 hours of the ICU stay.

Late onset pneumonia	Pneumonia that becomes clinically evident after the first 48 hours of the ICU stay.
Mechanical ventilation	Ventilation of the lungs accomplished by extrinsic means (mechanical ventilator).
Minor infection	Infections originating from the urinary tract, skin, superficial wounds, gastrointestinal tract and vagina.
Nosocomial infection	Infection that is not present or incubating on admission to hospital.
Oropharyngeal	Relating to the area of the pharynx between the soft palate and the epiglottis.
Pulmonary artery catheter	Catheter inserted into the pulmonary artery to measure pulmonary capillary wedge pressure (PCWP) and thus evaluate cardiac function in cardiogenic, hypovolaemic and septic shock.
Serious infection	Infections originating in the lungs, central nervous system, abdominal cavity or bloodstream. (Also 'major infection')
Tracheal aspirate	Fluid withdrawn from the trachea ('windpipe') by suction, for microbiological culture.
Tracheostomy	Creation of an opening into the trachea through the neck, with insertion of an indwelling tube to facilitate passage of air or evacuation of secretions.

Abbreviations

ADHs	Additional doctors' hours
APACHE	Acute physiology and chronic health evaluation
CPAP	Continuous positive airways pressure (artificial ventilation mode)
CCU	Coronary care unit
CSSD	Central sterile supplies department
DGH	District general hospital
DRG	Diagnosis-related group
g	Gramme
GNAB	Gram negative aerobic bacteria
HDU	High dependency unit
ICS	Intensive Care Society
ICU	Intensive care unit
iv	Intravenous
LTH	London teaching hospital
LYG	Life years gained
mg	Milligrammes
ml	Millilitres
MPM	Mortality prediction model
MRSA	Multiresistant *Staphylococcus aureus*
MU	Mega units
NHSME	National Health Service Management Executive
NST	No significance test reported
OFS	Organ failure score
PA	Pulmonary artery
PMH	Previous medical history
PTA	Polymixin E, tobramycin and amphotericin-based SDD regimen
QALY	Quality adjusted life year
QoL	Quality of life

Abbreviations (cont.)

RCT	Randomised controlled trial
qds	Four times a day
SAPS	Simplified acute physiology score
SCARRF	Severe combined acute renal and respiratory failure
sd	Standard deviation
SDD	Selective decontamination of the digestive tract
SEM	Standard error of the mean
tds	Three times a day
TISS	Therapeutic intervention scoring system
WFI	Water for injection

Chapter 1: Introduction

This thesis explores the issue of economic evaluation in intensive care medicine, in general, and the economic evaluation of prevention of ICU-acquired pneumonia with *selective decontamination of the digestive tract* (SDD), in particular.

Intensive care medicine dates from the 1950s when long term artificial ventilation was developed for polio victims [Hulstaert *et al*, 1990]. Since that time it has developed into a discrete clinical discipline. Intensive care has many different interpretations in society, as most people have no first hand experience of it. To the layman, it is regarded as the 'winning technology, through which miracles of modern medicine may be performed' [Hulstaert *et al*, 1990]. To clinicians, the intensive care unit is where the most serious cases are sent in the hope that medicine will win against heavy odds. To policy-makers, intensive care is the endless consumer of non-budgeted resources, making constant financial demands, often supported by subjective and emotional arguments from clinicians and patients.

Modern intensive care medicine is a rescue therapy, rather than 'cure' or 'care' [Jennett, 1986]. Its widely accepted aim is the 'restoration to normal of vital organ function in order to gain time to treat an underlying disease and provide an appropriate quality of life for the future' [Hulstaert *et al*, 1990]. To achieve this, there are three categories of intensive care, defined by the European Society of Intensive Care Medicine [Miranda *et al*, 1990]. The *recovery room* is where patients are observed and treated in the immediate postoperative period. The *high dependency unit (HDU)* provides a higher level of nursing care and medical consultation than is required on a normal ward. The *intensive care unit (ICU)* is where continuous specialised nursing and medical

care, combined with dedicated equipment, is available for the normalisation of vital organ function, without time limit.

ICUs were developed with the aim that concentration of resources would lead to economies of scale and improvements in quality of care [Hulstaert *et al*, 1990]. In the last thirty years there has been unrelenting expansion and development of intensive care medicine. One day on an ICU can cost up to four times as much as a day on a normal ward. Reported average costs per day on British ICUs can exceed £1000 [Singer, 1991].

The UK has a lower level of ICU provision than the rest of Europe and the USA. In the UK, only 2.6% of adult acute hospital beds are allocated to ICUs. Denmark has the highest European provision of 4.1% [Miranda *et al*, 1990]. In comparison, 7 to 11% of acute care beds in the US are ICU beds [Osborne *et al*, 1994]. In 1992, intensive care medicine accounted for 15-20% of US hospital costs, or 1% of their GDP [Osborne *et al*, 1994]. In Britain, only 0.05% of GDP is spent in intensive care medicine. It is, of course, difficult to draw direct comparison between British and American health care provision due to differences in medical culture and health service funding methods. However, the presence of a twenty-fold divergence between the UK and the USA warrants further investigation into reasons for existing provision levels.

Achieving the optimal or most 'efficient' level of ICU provision requires information on resource use associated with ICU provision, and the level of benefit incurred by the target patient population. In the UK, there is a growing awareness that purchasers require information about how best to allocate their resources in an NHS increasingly focusing on cost-effectiveness. However, optimising ICU resource allocation is limited by the lack of cost effectiveness evidence available [Metcalfe *et al*, 1995].

This is because, like many high technology medicines, and health technologies in general, intensive care medicine was introduced without prior evaluation. There is no overriding legislation to control the purchase and use of heath care technology in the UK, and until recently, little evidence of a coherent policy for health technology assessment. However, in recent years, the need to control the introduction of new technologies has become more widely appreciated, partly due to more organised activity overseas [Spiby, 1994]. The response to this in the UK is the creation by the NHS management executive (NHSME) of a standing group on health technology assessment [NHSME, 1994]. Their recommendations for evaluations of interventions are based on the premise that 'without reliable information about the effects of health technologies, soundly based decisions cannot be made about the deployment of resources' [NHSME, 1991].

To date, there has been only sporadic clinical and economic evaluation of intensive care. A major barrier is that it is established (in the minds of the medical profession and society) as a 'life saving' technology and it would now be considered unethical to randomise patients to receive intensive care, or not [Miranda *et al*, 1990]. There is no doubt that many severely ill patients benefit from admission to an ICU. However, intensive care medicine consists of many technologies used in a wide range of patients. To achieve the optimal level of provision, it is necessary to evaluate whether individual interventions and technologies used in intensive care are being directed at patient groups most likely to benefit, and whether those technologies are being used optimally in those patients. This divides the issue of efficiency into *allocative* and *technical* efficiency. Allocative efficiency exists when there is the most efficient, or optimal, level of ICU provision within health care provision in general [Drummond *et al*, 1987]. Technical efficiency exists where those resources provided for intensive care are used to produce the largest net benefit possible.

Neither of these efficiency targets can be achieved without evidence on effectiveness. However, there is little published research in effectiveness of technologies used within intensive care. This is usually attributed to difficulties associated with doing randomised controlled trials (RCTs) in an intensive care environment. Due to the critically ill nature of ICU patients, it is more difficult to obtain ethical approval or patient consent. Patient groups are frequently either homogeneous but too small, or large but heterogeneous. Assessment of technical efficiency of many interventions may be precluded if economic evaluation is only conducted as part of an RCT. The NHSME advisory group on health technology assessment suggested that alternative methods, such as use of observational data, could be used to 'demonstrate the effects of health technologies ... in some circumstances where randomised trials are not feasible' [NHSME, 1991]. Alternative methods of economic evaluation incorporate the development of models that have clinical and economic evidence attached to them from multiple sources, rather than from one RCT. The main difference is that data derived from multiple sources, rather than one source, are combined for use in analysis. These sources can be *primary* or *secondary*. Primary economic or clinical data are collected either within the framework of an RCT or from an observational study. The analysis is carried out on the same patient group that was used to obtain the data. Secondary data consists of published evidence. It is used in analysis of patient groups other than those originally used to collect the data. The use of modelling techniques for economic evaluation is used as an alternative to economic evaluations attached to RCTs. This alternative methodology could be particularly useful in intensive care medicine. Investigation is required into whether the methods are applicable to intensive care.

This thesis examines the application of modelling techniques in the economic evaluation of SDD, used to prevent ICU-acquired pneumonia.

The primary aim is to examine whether SDD can be demonstrated to be cost effective, using these techniques. The secondary aim is to examine whether alternative modelling methods of economic evaluation allow the derivation of cost/outcome ratios that can be used with as much confidence as those that would be derived from RCT-linked economic evaluations.

Chapter Two introduces the issue of economic evaluation of intensive care medicine. Drawing on published British and foreign evidence, the need for research into both allocative and technical efficiency is demonstrated. The methods used in economic evaluation are described. The evidence available on technical efficiency on intensive care and its technologies is examined.

Chapter Three focuses the issues raised in Chapter Two onto the specific clinical and economic issues surrounding ICU-acquired pneumonia and its prevention by SDD. The highly significant economic and clinical impact of ICU-acquired infection, particularly pneumonia, is described through a consideration of published evidence. Although SDD is a resource-intensive intervention, it may result in decreased resource use due to fewer episodes of pneumonia. To assess the cost effectiveness of SDD, economic evidence is required on the resource use and patient outcome implications of SDD and ICU-acquired pneumonia. This chapter concludes that the evidence available precludes making conclusions about the cost effectiveness of SDD. A formal assessment of costs and benefits is recommended.

Chapter Four, therefore, develops the framework for the economic evaluation of SDD. This chapter defines the economic question to be asked and employs decision analysis to develop a decision-analytic model upon which to base a formal economic analysis [Weinstein, 1980]. When the model has been designed, it is necessary to attach

clinical and economic evidence to it. This evaluation uses secondary data sources for this evidence. Systematic review techniques are used to extract evidence to derive incremental cost/outcome ratios. The sensitivity of conclusions drawn to variation in underlying parameters are tested using sensitivity analysis. This analysis suggests that, in general, the clinical data available is of high quality, but it is not always presented in such a way that allows direct application to economic evaluation. Also, improved economic and patient outcome data is required to improve the conclusions on the cost effectiveness of SDD. This thesis concentrates on the impact of the quality of economic data on the uncertainty around cost/outcome ratios. Collection of primary economic data should only be recommended under two conditions. The first is that there will be sufficient added value from the evidence collected in a primary study to improve upon the conclusions drawn by a secondary analysis. The second condition is that there is sufficient use, clinical interest or controversy surrounding the therapy that the results from a primary study will have an impact on decision makers.

Chapters Five to Seven report the acquisition of primary data on the economic impact of ICU-acquired pneumonia and SDD. To carry out an economic evaluation of SDD applicable to British practice, it is necessary to have information about clinical practice of SDD in Britain. Chapter Five describes the identification of British practice patterns and resource use associated with SDD through a national postal survey. Chapter Six describes the acquisition of primary bottom-up economic data arising from ICU-acquired pneumonia in two British ICUs, one at a London teaching hospital and one at a district general hospital. Identification of the impact of infection, particularly ICU-acquired pneumonia, on resource use is investigated in Chapter Seven. The impact of infections and confounding factors is handled quantitatively, using linear and logistic regression techniques, with reference to the effect on resource use and patient mortality.

Chapter Eight describes an economic evaluation of SDD that models the clinical and economic impact of SDD if it was to be implemented at the two ICUs investigated in Chapter Six. Economic evidence obtained in Chapters Five to Seven is applied to the decision-analytic model developed in Chapter Four. Conclusions on the cost effectiveness of SDD are derived for the two ICUs described. Sensitivity analysis is used to assess the robustness of conclusions to variation in underlying parameters. The 'added value' obtained from devoting resources to obtaining primary economic data is examined in this chapter. The *realisable* cost savings arising from the possible implementation of SDD at the two ICUs studied, compared with the theoretical values derived by this economic evaluation, are discussed.

Chapter Nine draws together the main points of the thesis. The extent to which the thesis has met its objectives through the methods used is discussed. The policy implications of the results reported in this thesis for the use of SDD in ICUs are examined. Finally, the wider implications of the use of modelling in economic evaluation in intensive care are considered.

Chapter 2: The Economics of Intensive Care

2.1 INTRODUCTION

Health care costs in general are rising for a number of reasons, including increase in population size and age, rising levels of service, new technologies and society's growing expectations of health services [Miranda *et al*, 1990]. There is a steadily increasing awareness that resources for health care are limited. Unfortunately, the possible uses of those resources far exceed their capacity. In this climate it is essential that intensive care provision should represent a balance between resource use and likelihood of benefit to patients.

The clinical objective of intensive care medicine is to maximise the incremental health gain it imparts upon the population it serves. This objective is achieved by increasing life expectancy and quality of life through clinically effective intervention. Clinical effectiveness exists where an intervention can be shown to improve either quantity or quality of life, or both, in research and practice. However, clinical effectiveness is a 'counsel of perfection in a real world which can never afford to be all things to all persons' [Reisman, 1993]. The scarcity of health care resources means that treating one patient necessarily means leaving another on the waiting list. In this context it is unethical not to ensure that these resources are used as efficiently as possible. Therefore, the economic objective of intensive care medicine is to meet the effectiveness objective, given the level of provision deemed affordable by the host hospital and the funding health service at large, thus achieving efficiency at the same time.

The aim of this chapter is to introduce the issue of efficiency in intensive care medicine and examine whether there is a need for

economic evaluation. The *social opportunity cost* of using scarce resources in one activity is the benefit forgone by not using them in the best alternative activity [Friedman, 1984]. The use of scarce resources in intensive care to improve the health of a group of individuals necessarily precludes their use in an alternative group of individuals. The benefit forgone by these individuals is the true opportunity cost of intensive care. The economic efficiency of intensive care can broadly be divided into *allocative* and *technical* efficiency. Intensive care can be considered to show allocative efficiency if diverting resources away from intensive care would result in more 'disbenefit' occurring in the intensive care population than benefit would be gained in other health care target populations. Allocative efficiency is considered more specifically within the context of an examination of the level of provision of intensive care in the UK, compared with other industrialised countries in section 2.2.

The second component of efficiency is technical efficiency. The need for investigation into technical efficiency is demonstrated in section 2.3. Technical efficiency in intensive care arises from the efficient interaction between inputs (intensive care patients), health care intervention processes and outputs (health outcomes). These are examined in the context of their impact on one another and on technical efficiency in sections 2.4 to 2.6. The economic evaluation of intensive care medicine is complicated because it is composed of a range of technologies. Therefore, section 2.7 examines the published evidence on the technical efficiency of these technologies. The evidence available is assessed in terms of quality. Reasons for the lack of economic evidence are suggested. Finally, the implications of the findings from this chapter for economic evaluation in intensive care are discussed in section 2.8.

2.2 ALLOCATIVE EFFICIENCY IN INTENSIVE CARE: AN INTERNATIONAL COMPARISON

Allocative efficiency exists on a number of levels [Williams, 1986]. In the British context, there are decisions to be made about allocation of Government resources between different public services, such as health, social services, education or defence. Within the health service, resources can be allocated to the primary, secondary or tertiary sectors. Within a hospital, different specialities compete for resources. Within each speciality there is a decision to be made about which patients should be treated [Drummond *et al*, 1987]. At each level of resource allocation, allocative efficiency is only achieved if the benefits incurred *maximally* exceed the opportunity cost. In practice, deciding on optimal levels of intensive care provision is very complex, due to arbitrary budget constraints, use of unevaluated technologies precluding assessment of cost effectiveness, pressures from clinicians, patients and families who may not recognise or accept when medical intervention is futile and the increasing threats of litigation. Varying influences of these factors have resulted in the level of provision being highly disparate in different countries [Miranda *et al*, 1990].

The UK has the lowest reported level of ICU provision of an industrialised country, and the USA has the highest. Table 2.1 illustrates the twenty-fold difference between the two countries in proportion of monies spent on intensive care in 1990.

Table 2.1 Intensive Care Costs per Person in Selected Industrialised Countries in 1990 [Metcalfe *et al*, 1995]

Country	HC[1] (% GDP[2])	GDP /CAP[3](£)	HC costs /CAP(£)	IC[4] (% HC)	IC costs /CAP(£)
USA	12.4	11634	1443	10	144.3
France	8.9	11805	1050	?5	(52.5)[5]
NZ	7.2	7211	519	?5	(26.0)[5]
Japan	6.5	13164	856	?5	(42.8)[5]
UK	6.1	9540	582	1	5.8

[1] Health care

[2] Gross domestic product

[3] Gross domestic product per person at 1990 market prices

[4] Intensive care

[5] Estimated intensive care costs as 5% of all health care costs

This section compares the levels of intensive care provision in the UK and USA to identify where the differences in resource allocation lie, *why* intensive care provision is so different, and to what extent more general health care provision structures impact upon this provision. An assessment of whether allocative efficiency in intensive care medicine is achieved by the two countries is not within the scope of this review. However, whether British or American levels of ICU provision can be considered more closely to approach allocative efficiency, on the strength of evidence available, is briefly examined.

The USA devotes twice as much of its GDP to health care provision as the UK (see Table 2.1). Therefore the difference in intensive care spending may reflect significant differences in health care provision in general. These differences in health care expenditure are usually attributed to methods of funding and provision of services. In the USA, health care costs are met largely by third party insurance. The

combination of third party payment, tax relief for health insurance and strong patient autonomy dominating the clinician/patient agency relationship effectively reduces barriers to resource intensive interventions like intensive care [Osborne *et al*, 1994]. Standard economic theory suggests that when people pay less than the full cost of what they buy, they will consume more than is socially optimal (unless their consumption benefits other individuals in the process) [Aaron, 1991]. This theory suggests that insurance payment systems induce excessive health care expenditure. Insurance is purchased to avoid the risk of unexpected expenditure but, because it provides a reduction in price at the time that care is purchased, it may have the concomitant effect of artificially increasing the demand for care [Feldstein, 1979]. The price is also increased as there is no incentive to 'shop around' for the best bargain.

The impact of excessive use of health care by an individual on insurance premiums is spread over the group as a whole. A vicious circle of more insurance claims leading to higher costs and higher costs requiring more insurance develops [Reisman, 1993]. This hypothesis is supported by Evans' [1984] comparison of US and Canadian health care spending trends from 1960 to 1982. From 1960 to 1971, funding methods were insurance-based for both countries and there was a comparable increase in health care spending from 5% to 7.5% of GDP [Evans, 1984]. The introduction of national public insurance coverage in Canada in 1971 initiated a period where health care costs did not rise as a proportion of GDP for ten years. During this period, health care in the USA was still funded by third party insurance and spending rose to 10.5% of the GDP.

The mechanism of insurance-funded health care leading to an increase in health care costs is particularly relevant in the area of high technology medicine. New techniques that are not demonstrably effective are more

likely to be taken up by hospitals funded by third party insurance than by those who are publicly reimbursed. However ineffective they are, they contribute to filling beds and inflating bill receipts [Reisman, 1993]. However, with the prediction in 1987 that the USA would be devoting 15% of GDP to health care by the year 2000, the issue of rationing health care is becoming more prominent [Aaron, 1991]. Aaron suggests that the elimination of health care interventions that produce 'little or no benefit' would immediately result in a reduction in spending of 30%.

It has been suggested that there is over-provision or inefficient provision of health care and intensive care in the USA. Equally it has been suggested that there is under-provision in the UK [Metcalfe *et al*, 1995]. However, the provision of health care in the UK is likely to contain as many structural and cultural barriers to efficient allocation of resources as the USA [Reisman, 1993]. The UK NHS is financed primarily from general taxation revenue and has a system of primary care provided by general practitioners (GPs) who effectively ration hospital-based services. The NHS and Community Care Act (1990) separated provision of health care from funding [Osborne *et al*, 1994]. Health authorities and fundholding GPs now purchase health care from the NHS or the private sector. In the UK, the clinician is the gatekeeper to health care, rather than the patient, as in the USA. In the UK, the agency relationship that exists between clinician and patient is different from the USA in that the clinician exhibits more autonomy. The clinician procures health care on behalf of the patient, taking on the responsibility of decisions regarding intervention. Issues implicit within clinical decision making that could compromise economic efficiency include decisions based on imperfect information; considerations of equity; pressure from the patient and fear of litigation [McGuire *et al*, 1988].

However, this agency relationship is also affected by the purchaser/provider split that now exists, as clinicians are under pressure

from both to produce cost effective health care [Ham, 1992]. The introduction of competition and associated cost consciousness to the NHS has profound implications for costly high technology specialities like intensive care medicine.

A natural consequence of international comparison, whether valid or not, is concern that ICU provision in the UK is inadequate [Metcalfe *et al*, 1995]. A King's Fund panel formed to investigate the level of provision of intensive care medicine in the UK concluded that there was not enough evidence on effectiveness or cost effectiveness of ICUs in the UK to answer any questions about optimal levels of provision [King's Fund Panel, 1989]. Metcalfe *et al* [1995] examined the provision of intensive care in England. They report wide variations in ICU provision around the country, wide ranges in occupancy rates and patient refusal rates[1]. On average, 6.7% (range 0 to 47%) of requests for admission to ICUs are refused. 70% of these refusals are because of lack of beds or nursing staff. Refusal rates are often used to imply that there is insufficient ICU provision in Britain. This is misleading because there is little evidence to confirm whether patients who are accepted onto ICUs are appropriate candidates for intensive care.

It is not possible, on the basis of the evidence examined, to make definitive statements about whether the USA or UK have achieved allocative efficiency in intensive care medicine. No evidence has been found that indicates differences in patient outcome between the UK and the USA. This may indicate either that there is no difference and the extra resources used in the USA do not generate better health outcomes, or simply that appropriate comparative studies have not been

---

[1] Patient refusal rates are recorded by most ICUs. When an admission to an ICU is refused, for whatever reason, the patient must be transferred to another ICU or maintained on a lower dependency unit until an ICU bed becomes free.

carried out. The barriers to efficient allocation of resources to intensive care in the US are patient autonomy; high litigation levels leading to defensive medicine; the perverse incentives associated with third party insurance; and lack of effectiveness or cost effectiveness evidence. The barriers in the UK are the gatekeepers to ICUs (non-ICU clinicians) not being exposed to the true cost; clinician autonomy; until recently the inability to provide cost figures for intensive care; and the lack of evidence for effectiveness and cost effectiveness. In both systems, the consumers of intensive care, patients and clinicians, are not exposed to the true economic cost due to the funding mechanisms within their health care systems, and they make their decisions based on imperfect information. So, although the health care systems in the UK and US have resulted in highly disparate levels of intensive care provision, the barriers to allocative efficiency are similar.

2.3 TECHNICAL EFFICIENCY IN INTENSIVE CARE

Technical efficiency arises from the optimal combination of inputs and resource use to produce the maximum output [McGuire *et al,* 1988]. McGuire *et al* suggest that, given a fixed level of input, it can be achieved in four ways:

1. increasing output at a given level of resource use;
2. maintaining output at the same level whilst decreasing resource use;
3. increasing resource use and output, increasing output at a higher rate and
4. decreasing resource use and output, decreasing resource use at a higher rate.

Technical efficiency of intensive care exists, for a given level of service provision, when the maximum net benefit is derived from the resources available for use [Friedman, 1984]. Intensive care is a collection of technologies and interventions. To assess the technical efficiency of intensive care, it is necessary to know how efficient are the individual technologies, to allow optimal combinations. The input, process and outcome of intensive care and their relationship with technical efficiency are addressed in the following three sections.

2.4 INPUT: THE PATIENTS

For intensive care medicine to be effective, it should only be used for those patients who will benefit. Failure to exclude patients for whom intensive care medicine is either unnecessary or unsuccessful wastes resources and obscures the benefit of effective therapies. An estimated 95,000 patients were admitted to 257 UK ICUs in 1992 [Metcalfe *et al*, 1995]. With a patient population of this size, in such a costly speciality, it is essential that only appropriate patients are admitted. Admission guidelines for ICUs were defined by the US National Institute of Health Consensus Conference [Ayers *et al*, 1983]:

1. patients with acute, reversible disease for whom the probability of survival is low without ICU but high with it;
2. patients whose probability of survival is low without ICU care and uncertain with such care and
3. patients admitted to an ICU because they are at risk of becoming critically ill so to prevent serious complications or respond promptly to any complications that might occur.

Patients for whom intensive care is not considered appropriate are those admitted for monitoring that could be carried out equally well elsewhere, in a less costly environment, and those that are so severely ill that they will die with or without intensive care intervention [Miranda *et al*, 1990].

Distinguishing between appropriate and inappropriate patients requires characterisation of the intensive care population. The characteristics most commonly used are 'severity of illness', diagnosis and age.

Severity of illness measurement is used as a routine method of patient characterisation because patients are admitted to intensive care as a consequence of the severity of their condition, rather than the diagnosis. The most widely used and extensively validated severity of illness measure is the Acute Physiology and Chronic Health Evaluation (APACHE) II score developed by Knaus *et al* [1985], which has recently been validated for use in the UK [Rowan *et al*, 1993]. It combines a measure of previous health status with the current acute health state. APACHE II was designed to indicate severity of illness of groups of patients to enable comparison between units and between patient groups in clinical trials. The prognosis attached to severity of illness indicators for different diagnoses has been derived. The overall correct classification rate of hospital survival for APACHE II is 86%, precluding its use for individual patient prognosis [Knaus *et al*, 1985]. It does, however, allow stratification of patients and provides a standard parameter which allows comparison between ICUs.

Diagnosis and age are also used to characterise patient groups. Diagnostic categorisation of ICU patients is complex because most have multiple diagnoses. Precise diagnostic categorisation of patients can lead to many diagnostic groups containing small numbers of patients. Also, lack of continuity in diagnostic categories makes comparison between units or studies difficult [Miranda *et al*, 1990]. Therefore, it is rarely relied upon alone to characterise an ICU population. Age is often

used in description, but rarely as a barrier to ICU admission. As the age of the population increases, the age of people requiring intensive care is rising. Nicholas *et al* [1987] reported that 24.1% of their French ICU population was over 65 and 7.9% was over 75. Increased mortality is found in older age groups but this increase is lost once severity of illness and previous health status are controlled (Nicholas *et al* [1987], Wu *et al* [1990], Pesau *et al* [1992]). The argument that elderly people do not benefit from intensive care is therefore not supported by empirical evidence, but the effect on life-years or quality-adjusted life years gained may have implications for economic evaluation.

Other characteristics such as surgical category, race or smoking status provide useful information when comparing intensive care populations. Patient characteristics may have a significant impact on the resource use of an ICU due to their effect on the process of care. Differences in resource use and patient outcome between ICUs are more comprehendible when differences in patient populations are known [Knaus *et al*, 1985]. Comparison of effectiveness and cost effectiveness studies from different centres can be validated or precluded by information on types of patient populations used.

2.5 PROCESS: THE COST OF INTENSIVE CARE

The process of intensive care medicine utilises a range of technologies, specialised staff and vast quantities of consumables. For the purposes of economic analysis it is necessary to have information on the resource use associated with that process and costs associated with that resource use. Costs should have the following characteristics [Drummond *et al*, 1987]:

1. They should comprise all relevant resource use associated with interventions, on an individual patient or 'bottom-up' basis.

2. They should reflect the true economic cost of that service.

3. They should have explicit sources, components and methods of collection or derivation. Whether the *short* or *long run* is being considered should be stated and justified. Explicit handling of fixed, semi-fixed and variable costs is necessary. Any uncertainties surrounding methods should be explicitly stated and tested for importance using sensitivity analysis.

4. The perspective of the study should be stated. This affects whether intensive care, hospital, health sector or indirect costs are included, and should be explicitly stated.

A review of the literature [1976 to 1994] provided twenty-two studies on the cost of intensive care, one unpublished study [Gyldmark, 1993] and one report [South Australia Health Commission, 1994]. Results from these studies are summarised in Table 2.2. Costs per ICU patient reported in the studies vary widely, due to technological development over time and variations in patient groups, unit characteristics and clinical practice. Also, methodological variation in costing intensive care increases apparent variation in costs, but does not reflect actual resource use differences. This section assesses to what extent the methods used by the studies vary and whether they meet the methodological guidelines described above.

Table 2.2 Summary of Methods Used to Estimate ICU Patient Costs in Published Studies

Study	No. and type of patients	Resource use recording method and cost source	Mean patient cost
Cullen *et al* [1976] US	226 Class IV[1]	Retrospective bottom up charges for hospital stay	$14304 (no sd)
Davis *et al* [1980] US	100 ventilated	Retrospective bottom up charges for hospital stay	$12300 (SEM 800)
Thibault *et al* [1980] US	2693 medical	Retrospective bottom up charges for hospital stay	Not reported
Detsky *et al* [1981] US	1831 ICU/CCU	Prospective bottom up charges for hospital stay [V]	$5393 (no sd)
Parno *et al* [1982] US	558 consecutive	Prospective bottom up charges for hospital stay [DV]	$9491 (no sd)
Wagner *et al* [1983] US	96 surgical	Prospective bottom up charges for ICU stay [DV]	$3378 (no sd)
Bams *et al* [1985] Holland	238 consecutive	Retrospective top down average bed days for ICU stay [DSV]	None reported
Girotti *et al* [1986] Canada	67 randomly selected	Prospective bottom up charges for ICU stay [DSV]	$5566 (no sd)
Sage *et al* [1986] US	387 consecutive	Retrospective top down charges for hospital stay	$23327 (sd=1184)
Slatyer *et al* [1986] Australia	100 consecutive	Prospective bottom up, charges and costs for ICU stay [SV]	$1357 (sd=2676)
Loes *et al* [1987] Norway	961 consecutive	Retrospective, top down, average bed days for hospital stay	US$5760 (no sd)

Table 2.2 (cont.)

Author	No. and type of patients	Resource use recording method and cost source	Mean patient cost
Thoner *et al* [1987] Norway	249 ventilated surgical	Retrospective, top down, average bed days for ICU stay	$22823
Shiell [1989] UK	200 consecutive	Retrospective, bottom up, top down costs & charges[DSV]	£1950
Borlase *et al* [1991] US	100 consecutive surgical	Retrospective bottom up charges for hospital stay	$66174
Gilbertson *et al* [1991] UK	156 (30% in SCARRF[2])	Prospective bottom up costs for ICU stay [DSV]	£7053
Ridley *et al* [1991] UK	20 consecutive	Prospective bottom up costs for ICU stay [DSV]	£1980
Chelluri *et al* [1992] US	34 > 85 yrs old	Retrospective bottom up charges for hospital stay	$34738
Havill *et al* [1992] New Zealand	30 post cardiac surgery	Prospective bottom up costs for ICU stay [DSV]	NZ$2948
Gyldmark [1993], Denmark[3]	201 surgical	Prospective bottom up costs for ICU stay [4SV]	Dkr 38740
Ridley *et al* [1993], UK	90 consecutive	Prospective bottom up costs for ICU stay [DSV]	£3029

Table 2.2 (cont.)

Author	No. and type of patients	Resource use recording method and cost source	Mean patient cost
Cohen *et al* [1993], US	45 >80 years old, ventilated	Retrospective bottom up charges for hospital stay	$47543
Schapira *et al* [1993], US	147 cancer	Retrospective bottom up charges for hospital stay	None reported
SA Health Commission [1994], Australia	1445 (3 ICU's)	Prospective bottom up costs for ICU stay [DSV]	$7027 (184-63738)
Singer *et al* [1994], UK	272 (1988, 1991 study)	Prospective bottom up costs for ICU stay [DSV]	£1008 (1988); £1149 (1991).

[D] = departmental overheads,

[S] = staff costs,

[V] = variable costs

[1] Cullen's Class IV patients (see Appendix 2.1);

[2] SCARRF Severe combined acute renal and respiratory failure;

[3] Unpublished study;

[4] Overheads explicitly excluded;

[5] Resource use recorded and unit costs attached

2.5.1 Top-Down Versus Bottom-Up Costs

The two ways of collecting costs are either 'top-down' or 'bottom-up'. Top-down studies use the total budget to produce average costs per bed day. ICU costs per patient have been reported by four studies using this method (see Table 2.2). This method assumes that all patients have similar diagnoses, severity of illness, treatment and constant therapeutic intensity throughout the stay. The main limitation of this method is that the inter-patient variation in resource use due to interventions or severity of illness is not detected, so that the costs are not sensitive enough to be useful in an economic evaluation. Most costing studies examined reported their costs as 'bottom-up' costs or charges. Bottom-up costs are patient-specific, so reflect interpatient variation. However, eleven studies did not separate ICU costs from total hospital costs, severely limiting the usefulness of their data.

2.5.2 Use of True Economic Cost

True economic cost takes into account all the cost associated with an intervention, not just acquisition market prices. Whilst empirical determination of true economic cost is complex, cost data needs to reflect true economic cost as closely as possible. In a nondistorted market prices provide an approximation of the value placed upon a resource. In a distorted market environment like a health service, estimation of true costs is not straightforward as normal price mechanisms are rarely present. Thirteen of the studies examined in this review are from the USA and all use hospital charges. The reason for this is that they are already collected as part of the hospital billing system, so are easily accessible. In the USA, hospitals are reimbursed by private insurers on the basis of a fixed price per unit for each type of service provided [Evans, 1984]. Such charges often depart substantially

from actual costs of production. This is because hospitals cross-subsidise losses on some services with profits on others, while running an overall surplus on operations to finance new growth [Feldstein, 1981]. These charges do not reflect the true economic cost of the service, although they have an obvious operational function, so should not be used in economic evaluation.

In the British NHS, prices for all health care services are now necessary for contracting. Market prices are available for components of the services, such as salaries, drugs and equipment costs and these will generally provide good approximations to true cost. However, prices charged by hospital departments for their services have often been criticised for bearing little resemblance to the true cost of the service [Drummond *et al*, 1987]. Due to the introduction of an explicit purchaser/provider split in the UK NHS in 1990, providers have to attach costs to services, many of which have never been explicitly costed previously. To standardise methods used to attach prices to hospital services, 'Costing for Contracting' recommendations were published by the NHSME in 1993 [Reeves, 1993]. The National Steering Group on Costing [Reeves, 1993] made the following recommendations on costing methods:

1. prices should be based on actual costs;
2. costs should be established on a 'full cost of treatment' basis (that is, including all relevant variable, semi-fixed and fixed costs);
3. there should be no planned cross-subsidisation between specialities, procedures and contracts and
4. the proportion of costs allocated as 'overheads' should be minimised to improve precision of costs.

Implementation of these guidelines should improve the quality and reliability of costs reported by centres. It should also make comparison between centres more valid.

The final requirement when considering true economic cost is a consideration of adjustment of costs for differential timing [Drummond *et al*, 1987]. Although comparisons in an economic analysis take place at one point in time, costs are not usually incurred at one point. Therefore, future costs should be reduced or *discounted* to reflect the fact that costs incurred or saved in the future are not considered to weigh so heavily as costs incurred in the present. This is due to the existence of *time preference*, whereby individuals prefer to have their resources now so that they can benefit from them. Discount rates, if used, need to be explicitly quoted. They can be government recommended rates (6% in the UK) or be consistent with current practice (such as 5% as used in the New England Journal of Medicine).

2.5.3 Source and Components of Cost Parameters

It is necessary to define which cost parameter is being considered in an economic evaluation. The *total cost* of intensive care, for a given unit of time, is the whole cost of producing a particular quantity of output from intensive care in that time period. In intensive care, that output is the patients treated and the quantity of output is the patient throughput, or activity of the unit. In the *short run*, total cost is made up of *fixed* and *variable* costs. Fixed costs do not vary with the quantity of output in the short run. In fact, the short run is defined as the time over which fixed costs do not vary [Lipsey, 1983]. These costs have either been incurred at the beginning of the short run period so are 'sunk costs', or they are incurred independently of activity levels. In both cases they are unaffected by activity. Short run variable costs do vary with activity.

The short run total cost of an intensive care patient includes both fixed and variable costs. However, admitting another patient to the ICU increases the total variable cost to the ICU, but has no effect on the fixed cost. Therefore, the variable cost of that extra patient is the short run marginal cost to the ICU of treating one more patient.

In the *long run*, there are no fixed costs. This period of time is long enough for the inputs of all factors of production to be varied [Lipsey, 1983]. In the long run, the ICU can make the decision to change its activity level. This will lead to changes in the short run fixed costs to accommodate this change. Therefore, in the long run, short run fixed costs can be considered as variable costs. So, the long run marginal cost of treating one more patient on the ICU includes the short term fixed cost of that patient. Therefore, the short run total cost of a patient is equivalent to the long run marginal cost of that patient.

In economic evaluation it is necessary to define whether the impact of the intervention is being examined *via* marginal or average costs in the short or long run. If an intervention has a significant impact on the length of ICU stay of patients, this changes the activity of the unit in the long run. It may be considered necessary to alter the capacity of the ICU to accommodate this change in activity. This incurs changes in the levels at which fixed costs are set for the next short run period. To give an indication of the change in levels of costs required, it is necessary to examine the incremental effect of the intervention on short run fixed costs. The short run total cost, equivalent to the long run marginal cost, provides this information. Consequently, this is the cost parameter more useful for policy makers. So, costs in intensive care should contain both these fixed and variable components. These are described in detail below. An intermediate category, *semi-fixed* costs, is also described.

2.5.3.1 Fixed Costs

In the short run, fixed costs are those incurred whether patients are treated or not. They consist of ICU-specific fixed costs such as maintenance of equipment. Other fixed costs are hospital overheads that are costs not only to the ICU, but to the hospital.

The two major components of ICU and hospital fixed costs are capital costs and overhead costs. Capital costs occur when major capital assets such as ventilators or defibrillators are purchased. The two components of capital costs are opportunity costs of capital assets (that is, the lost opportunity to invest the sum in another venture) and the depreciation over time of the asset itself [Drummond *et al*, 1987]. Capital expenditure is annuitised to reflect opportunity cost of the investment and depreciation of the asset. This annual sum is calculated by dividing capital expense by an annuity factor based on life expectancy and the discount rate. The life expectancy of an asset often does not equate to its physical life, being more dependent upon technological change. Other fixed costs are land opportunity costs and support services. ICU overhead costs are those incurred by support services and include catering, portering and laundry, general, medical and nursing administration and the maintenance, cleaning and heating of the unit. Most of these costs are shared costs, that is the support services allocate their costs to the several departments that use them. The NHSME [1993] 'Costing for Contracting' guidelines recommended that precision of cost analysis would be 'enhanced' by charging 'a greater proportion of their costs directly as opposed to...overheads'.

There are many methods used for cost allocation. Double counting can occur if overhead costs are accounted for twice by different support departments. Terminology varies between studies and it is not clear which components have been included. Some recent studies have

handled this more explicitly. Ridley *et al* [1991] reported a daily fixed cost for ICU at £82.29 (10% of total cost per patient), listing all the components they include, methods of allocation and source of cost.

2.5.3.2 Semi-Fixed Costs

Semi-fixed costs remain unchanged over a range of activity. Given sufficient changes in activity, they increase or decrease. The principal example is staff costs. If activity increases temporarily, short term adjustment can be made by using temporary staff. Long term increase or decrease in activity requires adjustment to resource levels determined for the next short run period.

Methods of retrospective allocation of staffing costs to patients range from very insensitive, that is, allocation by occupancy to give an average cost per day, to very sensitive, by assigning exact nursing time to all activities. Methods of nursing staff cost allocation have a significant effect on overall patient costs because they often comprise half the total cost [Gilbertson *et al*, 1991]. Use of an overall average cost does not reflect that patients on intensive care demand wide ranges of intensity of care. The most accurate, but time-consuming, way is to time each intervention and assign a nursing cost to it [Slatyer *et al*, 1986; Crew *et al*, 1987]. The two most commonly used workload indicators are the Therapeutic Intervention Scoring System (TISS) [Cullen *et al*, 1974] and the Intensive Care Society (ICS) Dependency Scoring System (Appendix 2.1).

Allocation of costs of staff from other departments, such as radiologists or pharmacists, can be done on a cost for time basis. Medical staff time is more complex to cost. This is because a patient may be attended by many clinicians during the ICU stay and medical treatment is not

confined to the bedside. Some studies include medical costs as fixed costs [Dick *et al*, 1992; Gilbertson *et al,* 1991] and some as semi-fixed costs [Ridley *et al* 1991, 1993]. However, Dick *et al* [1992] found no correlation between therapeutic intensity and total physician activities, so medical staff time could be treated as a fixed cost.

2.5.3.3 Variable Costs

Variable costs are incurred from a patient's treatment. This includes disposables equipment, diagnostic tests, drugs and blood products, ventilation costs and so on. Variable costs increase with treatment intensity [Dick *et al*, 1992]. Top-down costing studies cannot detect this patient variation. Bottom-up studies, using hospital charges or costs report wide variation between patients. Gyldmark [1993] reported the source of variable costs, using internal costs for diagnostic tests and market prices for drugs and blood products. Drugs and other consumables may have prices that vary between hospital due to the influence of buying groups, contractual agreements, quantity discounts and competitive bidding [Bootman *et al*, 1991]. If generalisability is important, it may be preferable to use standard prices. Methods used in assigning costs to services such as pathology or radiology can significantly affect end prices and should always be explicitly stated.

2.5.4 Perspective of Costing Study

It is necessary to state the perspective of the study as this determines which costs are included. If the cost to intensive care of treating a patient is the cost parameter under investigation, variable and semi fixed costs incurred on the ICU should be included. Intensive care and hospital overheads may or may not be included, depending on the

purpose of the costing exercise. If the cost to the hospital of treating an ICU patient is being examined, additional costs to the hospital must be taken into account. If the costs to the health sector of treating an ICU patient are derived, additional costs incurred in primary care need to be included. The only study reporting inclusion of direct costs to the health sector beyond hospital costs is Loes *et al* [1987]. These consisted of daily hotel costs of nursing homes, cost of home nursing, physiotherapy and medical consultations needed. Costs to the public sector included domestic help and disability pension payments.

More controversial and methodologically complex is the inclusion of indirect costs. Indirect costs can be more narrowly defined as the value of productive time lost due to morbidity and mortality [Drummond *et al*, 1987]. The value of productive time lost may originate from time out of work or housekeeping; time spent going to health care providers; time spent caring for the patient by relatives or paid carers; time forgone from leisure and other non-market activities [Hodgeson, 1994]. Time out of work tends to be the only indirect cost that can be reliably calculated from data. The use of production gains can, however, tacitly place a higher value on services catering for employable people rather than the elderly or children. There are many methodological difficulties associated with indirect costs so they are often not included. Hodgeson [1994] suggests that cost effectiveness ratios are usually higher without them. Empirical study has shown that indirect costs play an important role if health care programs produce health effects in the short term, if short term absence from work is significant and the target population is mostly employed [Koopmanschap *et al* 1994]. Therefore they may have a significant impact on intensive care costs. Pure cost effectiveness analysis would not include indirect costs because a benefit expressed in monetary terms introduces elements of cost benefit analysis.

Related to indirect costs are unrelated downstream medical costs [Hodgeson, 1994]. When medical intervention increases life expectancy, costs are incurred in the added years for illness and disease unrelated to the intervention. Downstream costs should be included when the perspective is that of the health care provider. Exclusion understates the full economic costs of an intervention. No published studies of ICU were found that reported indirect or downstream medical costs.

2.5.5 Predictors of Resource Use

This section examines the published evidence for predictors of resource use. Most costing studies report that a few patients account for disproportionately high levels of resource use. Shiell [1989] reported 10% of patients accounting for 45% of costs. Predictors of resource use identify those patients that are likely to be resource intensive. They can also be used as proxies for individual patient costing in economic evaluation. Predictors that have been investigated in the literature are diagnosis, age, severity of illness, therapeutic intensity and length of stay.

Diagnosis has been investigated for impact on resource use. Studies report ranges of costs for different diagnostic groups but comparison between studies is limited by inconsistent definitions. The assumed relationship of diagnosis with resource use is used in the reimbursement of hospitals in the USA. Patients are categorised by the system of diagnostic related groups (DRGs). These contain conditions regarded as sufficiently similar to be treated in the same way, and thus consume similar amounts of resources. They are thus considered to be isoresource groups. However, their use in intensive care is limited as they are insensitive to the impact on resource use of severity of illness.

Kreis *et al* [1983] reported that only 31% of hospital charges were reimbursed by DRG payment for trauma patients. Bekes *et al* [1988] reviewed the 151 most severely ill patients admitted to their ICU, finding that expenses per patient were $24098 higher than the DRG reimbursement. SA Health Commission [1994] reported that Australian DRGs accounted for only 26.8% of resource use variation. They all concluded that DRGs could not stratify severity of illness sufficiently specifically to reflect extra resources required to treat the most severely ill patients.

Age has also been investigated for impact on resource use. Fedullo *et al* [1983], Nicholas *et al* [1987] and Thoner *et al* [1987] reported no increase in cost per patient with age. However, hospital mortality increased with age, so the cost per survivor increased significantly with age from US$26600 in patients under twenty to US$77900 in patients over seventy [Thoner *et al*, 1987].

Severity of illness could be expected to have an effect on resource use. Prior to the introduction of APACHE II, studies reported that non-survivors were more costly to treat than survivors [Cullen *et al*, 1976; Detsky *et al*, 1986]. Civetta *et al* [1990] reported that APACHE II scores did not predict resource use for individual patients or for the whole unit. Prognostic uncertainty is reported as an indicator for high resource use by Detsky *et al* [1986] and Rapaport *et al* [1990]. The highest resource use is by patients who are predicted to die but live, or are predicted to live but die.

Measures of intervention intensity have been examined for their impact on resource use. The relationship of TISS to resource use has been examined. In the TISS system, therapeutic interventions are scored according to intensity of involvement. The points acquired per patient per 24 hours are an indicator of the amount of nursing and medical care

that patient has received. Total TISS scores are reported by many authors to explain resource use [Cullen *et al*, 1976; Wagner *et al*, 1983; Slatyer *et al*, 1986]. Malstam *et al* [1992] found that predicted versus actual charge per TISS point were very similar (US$48 vs US$54).

2.6 OUTPUT: THE OUTCOME OF INTENSIVE CARE MEDICINE

Quantification of changes in health outcomes attributable to intensive care is essential to measure effectiveness and efficiency. This section outlines which outcome measures are required for economic evaluation. It then examines the published evidence to assess what outcome measures have been investigated.

The mode of outcome measure defines the type of economic evaluation employed [Drummond *et al*, 1987]. Cost benefit analysis quantifies outcomes in monetary terms. It requires the explicit evaluation of non-financial benefits and burdens in monetary terms. This is simpler for some measures such as loss of earnings, payment for help and cost to the health service of treatment. More difficult is attaching monetary values to disability, distress, uncertainty or threat to life. Cost effectiveness analysis is often used in preference to cost benefit analysis. This allows one health outcome parameter to remain in nonmonetary terms, such as mortality or life years gained. The cost expended to attain one unit of this outcome is the cost effectiveness ratio. Cost utility analysis is used where multiple measures of outcome are merged into one utility measure [McGuire *et al*, 1988]. Cost utility analysis requires combination of mortality with morbidity measures into a single utility measure. This section, therefore, examines whether valid morbidity and mortality measures have been investigated for use in cost effectiveness analysis. Evidence on utility changes due to intensive care

is examined. Whether cost utility analysis in intensive care with current available evidence is possible is explored.

2.6.1 Outcome Measures: Mortality

This section examines the range of mortality measures that are used in intensive care medicine and their applicability to economic evaluations. Mortality is not generally considered to be a useful outcome measure for health care interventions due to its dichotomous nature and low frequency. However, in intensive care the principal short term aim is to avert death in order to treat a reversible but life-threatening condition. Therefore, deaths occur more frequently and have more validity as an outcome measure than they might have in other therapeutic areas. Because of this, mortality rates are often used as intensive care performance indicators, especially in the USA [Knaus *et al*, 1985]. However, mortality has been demonstrated to be much more closely linked to admission severity of acute illness and chronic health states than to organisational factors [Knaus *et al*, 1985; Zaren *et al*, 1988]. There are different ways of expressing mortality. Unit mortality is least useful as patients frequently die in the hospital after ICU discharge, or are discharged from intensive care to die more privately on a ward. Hospital mortality is a more useful short term mortality outcome measure but does not reflect what effect intensive care has on the life expectancy of patients. Critical illness continues to shorten life expectancy for a considerable period after discharge, especially in older patients [Dragsted *et al*, 1986; Ridley *et al*, 1991]. Ridley *et al* [1994] reported that the risk of dying in the first year after discharge was 3.4 times higher than the general population. It was not until the fourth year that mortality risk returned to that of the general population. Currently there are no studies that follow a cohort of intensive care patients for the full course of their lives. It is not known what impact

intensive care has on life expectancy. Also, technologies change so rapidly in intensive care that this information would not be very useful by the time it was known. The incremental impact of intensive care on mortality or life expectancy will probably never be derived empirically as this would require an RCT of admission to intensive care.

Examination of the evidence demonstrates that most costing studies quote cost per ICU or hospital survivor as their outcome measure. Using standard life tables, some have calculated life expectancies and quote a cost per life year gained [Thoner *et al*, 1987]. The latter method is more economically robust than the former. However, valid economic evaluations must take into consideration the continuing effect that intensive care has on survival, as much as present evidence allows.

2.6.2 Outcome Measures: Morbidity and Quality of Life

This section examines the importance of using morbidity measures and quality of life tools in the assessment of intensive care outcome. The importance of using these measures as outcome measures, rather than just mortality or life expectancy, is stressed. A model expressing the impact of intensive care on quality of life is proposed. The issues around assessing a rapidly changing quality of life are examined and instruments appropriate for use in intensive care patients are explored. It discusses the problems associated with morbidity and quality of life measurement in this group of patients. The evidence available is reviewed. Finally, suggestions for priorities in future investigation in this area are proposed.

There is a consensus that intensive care outcomes must be evaluated in terms of quality of life (QoL), rather than just quantity [PAEEC, 1994]. Petros *et al* [1995] have called for morbidity measures to replace

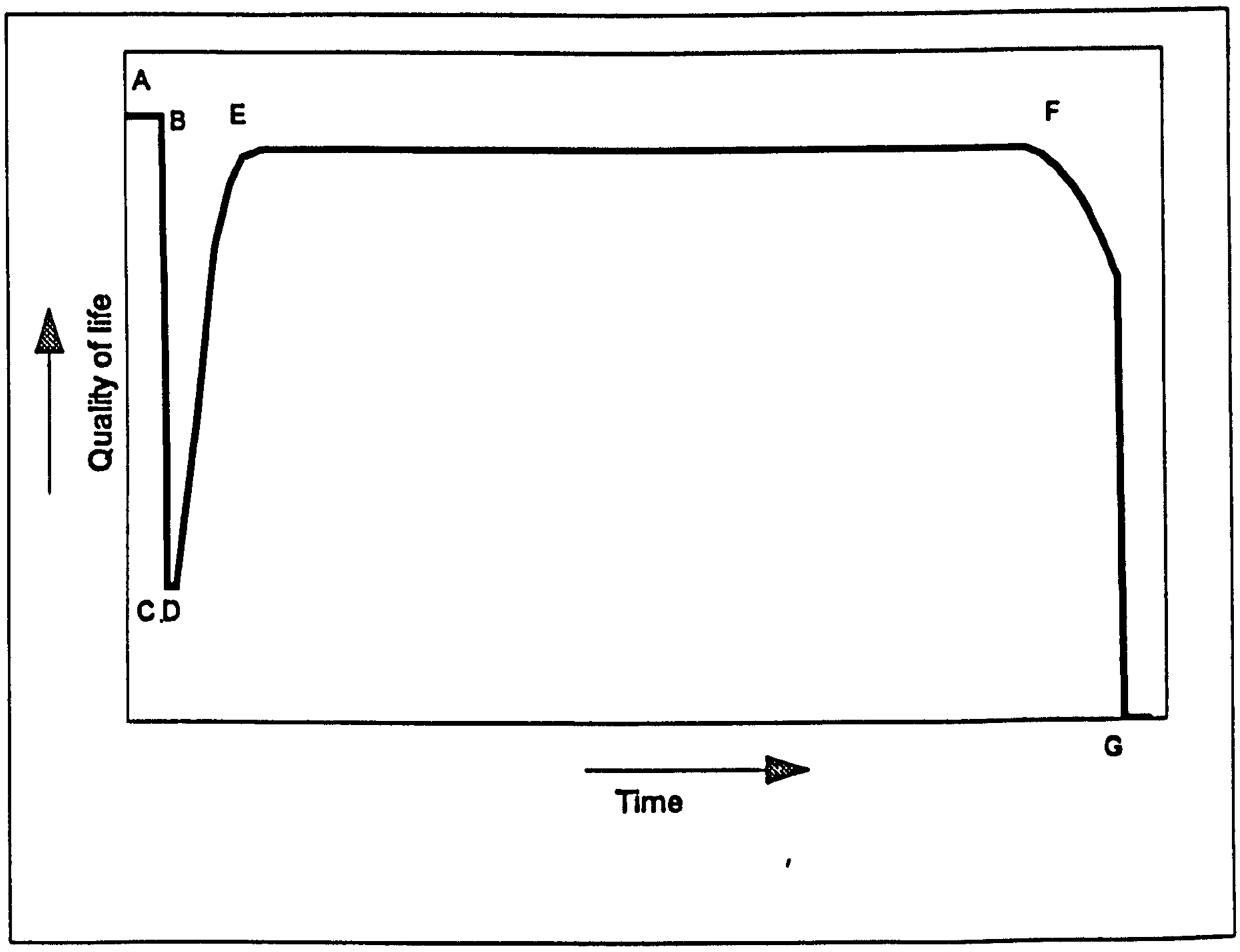
mortality as the primary ICU outcome measure. This is due to the inadequacy of mortality as an outcome measure. Proof of significant reduction in mortality as a result of interventions carried out in intensive care is often virtually unobtainable as the large homogeneous patient groups required are rarely available. Very large reductions in ICU-acquired infection rates due to prophylactic intervention [SDD Trialists' Meta-Analysis, 1993] have no demonstrable effect on mortality. Without information on impact on morbidity, it is more difficult to defend the introduction of this type of intervention.

There are many methodological problems associated with the assessment of morbidity and QoL in intensive care patients. Similarly to mortality measurement, the incremental effect of intensive care on morbidity is unlikely to be empirically determined. The incremental effects of different technologies within intensive care can be more easily assessed. Secondly, as intensive care is a rescue therapy, its aim is to return the patient to the same QoL after ICU discharge, so that there is as little decrease in QoL as possible. This means that QoL before and after the intensive care episode are required. Thirdly, in the assessment of a rescue therapy like intensive care, there is the issue of when to measure QoL, as it is likely to be highly labile immediately post-ICU admission.

To better describe the change in QoL over time from ICU admission, it can be depicted graphically. Figure 2.1 proposes a model that charts the course of an individual's QoL and the impact that an ICU admission has on it. AB is the chronic QoL prior to ICU admission. BC is the point at which a precipitating event occurs, resulting in ICU admission. CD is the QoL of the patient whilst on ICU. This assumes that QoL whilst on ICU is significantly decreased whilst on ICU due to the decreased level of consciousness, pain, fear and loss of autonomy associated with the ICU stay. DE is the recovery period of the patient, from ICU discharge,

through hospital discharge. E is the point at which the individual returns to a chronic QoL. This model does not assume that post-ICU QoL is equivalent to pre-ICU QoL (AB). FG marks the deterioration of QoL that occurs in the terminal stage of life. G is the point at which the individual dies. Premature death may occur at any point from B.

Figure 2.1 Hypothetical Model of Impact of Intensive Care on Quality of Life



This model demonstrates the fluctuating nature of the QoL of an intensive care patient. This affects the type of QoL measurement tool that can be used. Health related QoL tools should be reliable and valid, and the appropriate tool should be used for the situation. Apart from methodological soundness and empirical validity, the following criteria have been recommended by Buxton *et al* [1985] for a subjective health measure used to assess the impact of a high technology medical intervention.

1. sensitive to a wide range of health states, and appropriate to patients both before and after intervention;
2. the process of assessment acceptable to patients and any questions easily and unambiguously understood and
3. for purposes of comparison the measure should have been used, or should be likely to be used, in studies of other relevant groups.

Also, a QoL measure should be universally applicable to all intensive care patients, correlate QoL with medium and long term survival and be applicable after discharge to enable evaluation of interventions [PAEEC, 1994]. Disease-specific QoL tools are not generally appropriate because intensive care covers many conditions.

2.6.3 Quality of Life After Intensive Care-The Evidence

This section briefly reports to what extent the QoL of intensive care patients has been researched and whether the methods used fit the recommendations listed above. Sixteen QoL studies in intensive care were found and are summarised in Appendix 2.3. Most earlier studies used a range of unvalidated tools. Later studies have used validated measures such as the Spitzer QL index [Slatyer *et al*, 1986], Safar overall performance indicators [Loes *et al*, 1987] and the Nottingham

Health Profile [Shiell, 1989]. None of the tools used were validated for use in intensive care patients, apart from Patrick's perceived QoL score [Patrick *et al*, 1988]. The scope of health-related QoL measured ranges from purely functional measures which do not assess emotional or psychological domains at all [Cullen *et al*, 1976; Mundt *et al* 1988] to studies that have tried to cover all health-related domains of QoL [Patrick *et al*, 1988; Ridley *et al*, 1991].

Studies examining QoL prior to and after ICU report that, for most patients, QoL does not deteriorate significantly. Those patients in which there is deterioration are usually younger, previously fully employed patients with good previous health status who undergo trauma of some kind [Ridley *et al*, 1991]. Studies examining the impact of intensive care by comparing population data report worse QoL for ex-intensive care patients [Patrick *et al*, 1988; Shiell, 1989]. The importance of subjective measures is reflected by Patrick's QoL study. The patients' perceived quality of life was higher than the Sickness Impact Score and the General Well Being Score indicated. Patients who have undergone intensive care may rationalise their experience [Patrick *et al*, 1988]. If perceived QoL is not highly correlated with other measures of health outcome, then traditional measures of mortality and functional status are not sufficient for evaluating the benefits of intensive care.

Most studies measured QoL at a point in time after ICU admission so rate of recovery of QoL could not be assessed. Published evidence provides information on changes in chronic QoL only. QoL whilst on ICU, length of time to recovery and impact on life expectancy have not been investigated.

2.6.4 The Utility of Intensive Care

Quality of life measurement of intensive care patients does not allow cost utility analysis to be carried out unless the QoL measurements can be converted into utility measurements. This section discusses the issue of utility and its relevance to intensive care patients and economic evaluation of intensive care.

Utility measurement allows integration of mortality and morbidity effects, provision of preferences for both hypothetical and actual situations and incorporation of time and risk preferences of individuals [Drummond *et al*, 1987]. Utility can be directly measured using rating scales, 'standard gamble' and 'time-trade-off' techniques. Attaching relative weights or values to components of utility measures is methodologically complex. Reliable measures require labour-intensive interviews and utility measures for the same health state vary considerably across individuals [Feeny *et al*, 1989]. Alternatively, QoL measures can be converted to utility measures. This is not straightforward as they do not always correlate with one another [Tsevat *et al*, 1990].

In intensive care, decisions must be made about when to measure utilities and whose should be measured. Preferences expressed in a calm moment as a hypothetical issue are often different from those expressed in the urgency and confusion of a critical illness [Tsevat *et al*, 1990]. It can be difficult to make judgements about outcomes one has not experienced, especially concerning an alien and frightening experience such as intensive care. If preferences for outcomes are dramatically different *ex post* (preferences after experiencing intensive care) from *ex ante* (preferences before experiencing intensive care), then a choice about which preferences are appropriate must be made. Due to the potential instability of preference judgements over time, work has

concentrated on the changes to QoL that occur after intensive care. Also, prospective utility or QoL assessment is complicated by the inability of the patients to participate because they are too ill, or unconscious. Is it appropriate in this situation to use a surrogate decision maker such as a relative or doctor?

The most extensively empirically researched utility measure is quality adjusted life years (QALYs). QALYs adjust the number of years of life gained by the utility value (on a scale of 0 to 1) of the resulting level of health status [Drummond *et al*, 1987]. A comprehensive discussion of the methodological issues surrounding QALYs is beyond the scope of this review. However, four main concerns about QALYs are raised by Buxton [1992].

The first concern is that there is no consensus on the appropriateness of descriptive systems for health-related QoL. A multidimensional instrument is required that anchors health states into a scale from 0 to 1 (dead to full health). The first system by Rosser and Kind valued 29 health state combinations [Kind *et al*, 1982], but is now generally recognised to be inadequate in its ability to reflect all the main dimensions of health related QoL [Buxton, 1992]. Measures like the Nottingham Health Profile and the Sickness Impact Score have too many health states to realistically allow valuation. 'Euroqol' [The Euroqol Group, 1990] is a multiattribute scaling technique under development, where dimensions are hierarchically structured to reduce the extent of the valuation procedure. This measure is still being validated, but may prove to be applicable to ICU patients.

The second concern is that of validity and reliability of the process of valuation. Evidence suggests that different techniques give different answers and the same techniques can give different answers at different times [Gafni, 1991].

The third concern is the relationship of health state valuations to their duration, sequence or profile. This is particularly relevant where short health state durations, such as intensive care, are followed by long term health states. The utility attached to temporary health states is very difficult to measure because, if a future is added to the scenario, the preference value measured is actually that of a much broader scenario than the one which is claimed to be measured. If no future is added, the individual will assume a future so answers will not reflect only the preference towards the health state described [Gafni, 1991].

The fourth concern is whether risk and time preference are handled explicitly or implicitly by the valuation. If these factors are handled implicitly by the individual, answers may reflect an unquantifiable degree of risk and time preference. Time preference is handled explicitly by the use of discounting. Future health benefits tend to be discounted at the same rate as future costs, although there is debate about whether this is appropriate [Coyle *et al*, 1992].

For these reasons QALYs should be regarded with caution, but not dismissed until there is a 'better' practical alternative.

2.6.5 Evidence for Utility Measurement in Intensive Care

This section reports on the evidence associated with utility in intensive care. Very few ICU studies have used QoL tools appropriate for conversion to utilities. Ridley *et al* [1991] have reported converting their quality of life measurements to Rosser and Kind disability categories. They have not taken this any further, although it would be possible to convert this data to QALYs. There have been two studies on integration of quantity with quality of life changes due to ICU admission [Williams, 1986; Kerridge *et al*, 1995]. Using data from an ICU study by Cullen *et*

al [1984], Williams derived an estimate for QALYs gained by ICU admission, reporting three QALYs gained per critically ill admission. Kerridge *et al* [1995] derived a Rosser index QoL value for each survivor from a questionnaire. *Life years gained* (LYGs) was derived via the assumption that survivors at follow up had a life expectancy of 90% of age-specific life expectancy and a stable future QoL. The combination of LYGs and the Rosser index was used to derive QALYs. The discounted QALYs achieved ranged from 11.4 for asthma patients to 2.7 for pulmonary oedema patients. The discount rate used was 5%.

2.7 EFFICIENCY OF TECHNOLOGIES WITHIN INTENSIVE CARE

It has been demonstrated by this review that the technical efficiency of technologies within intensive care must be assessed. This section discusses this issue. It is necessary to have criteria with which to assess the quality of available evidence. The quality of studies that should be aimed for is outlined with a consideration of a hierarchical grading of evidence. The evidence for clinical effectiveness and technical efficiency in intensive care technologies is demonstrated to be lacking. Those studies available are assessed for the quality of their clinical and economic evidence. The limitations of only carrying out economic evaluations attached to RCTs is discussed. Alternative methodologies for economic evaluation are suggested.

2.7.1 The Quality of Clinical and Economic Evaluation

Cost effectiveness analysis can only be as good as the economic and clinical evidence that is used. Also, clinical and economic evaluations have resource implications of their own. Therefore it is essential that evaluations are designed as rigorously as possible so they produce the

'best' quality of evidence. It is possible to assess the quality of data available by examination of the design of a study. Eddy [1991] has proposed a system for assessing quality of evidence (see Table 2.3).

Table 2.3 Grade of Evidence [Eddy, 1991].

I	Evidence obtained from at least one properly randomised controlled trial
II-1	Evidence obtained from well designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence
III	Opinion of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Randomised controlled trials (RCTs) are the most useful design for determining the effects of an intervention on outcome. There is most control over confounding factors and a high degree of *internal validity*. However, excessive control of design can decrease applicability of study results to other settings (*external validity*). A rigorously carried out meta-analysis of RCTs is not included in this system, but would be considered to be a higher grade than one RCT alone due to the higher degree of external validity. Non-randomised controlled trials (*quasi-experiments*), Grade II-1, in which groups are selected by convenience, rather than random allocation, are subject to increased threat of bias to internal validity, especially patient-selection bias. The studies are carried out in more realistic settings which increases external validity and confounding factors can be controlled for by statistical methods. Below

this are observational studies (Grade II-2) where the use of an intervention is not manipulated by the researcher. Reality is observed and outcomes are interpreted. Cohort studies are more vulnerable to patient bias and confounding than RCTs, but have increased external validity. Other observational methods are cross-sectional surveys and case control studies (Grade II-3). Clinical series and professional opinion are least rigorous in design (Grade III). Whilst useful, this system concentrates only on design categories, not actual designs. A well designed large cohort study could be more meaningful than a small badly designed RCT.

Unfortunately, the quality of economic evaluations is more often decreased by the quality of the economic evidence, rather than the clinical evidence. The quality of economic evidence is affected by two main factors. The first is the costing methodology used, as discussed in section 2.6. The second factor is whether the evidence has been deterministically or stochastically obtained. *Stochastic* evidence is that collected from a random sample. The variables concerned have an observed mean and variance, that is, the uncertainty around point estimates can be quantified. *Deterministic* evidence consists of point estimates derived from expert opinion or assumptions. The variance, or uncertainty, of such data cannot be quantified. Both clinical and economic evidence can be deterministic or stochastic in origin. Ideally, an economic evaluation should use stochastic clinical and economic evidence. Data can be considered to be more *robust* if they are retrieved from a Grade I study, an RCT, as they are randomly obtained. This means that the data have internal validity and are stochastic, so statistical inference can be drawn, and uncertainty around point estimates is known. Economic evidence is much more likely to be deterministic in origin than clinical evidence, due to the more established methods used in clinical effectiveness studies [O'Brien *et al*, 1994].

Therefore, economic evaluations frequently contain a mixture of the two types of data. O'Brien *et al* [1994] put forward three scenarios:

1. *Deterministic analysis* where cost and effect variables are analyzed as point estimates due to limited, unsampled data. Deterministic point estimates of cost effectiveness so derived are subject to sensitivity analysis to explore the impact of uncertainty.

2. *Partially stochastic analysis* where effectiveness is estimated from clinical trials, expressed as a mean effect size with an associated variance, but analysis of costs is deterministic because data are non-sampled. This method is common in decision-analytic models of economic analysis. It is not appropriate to quote 95% confidence intervals around any cost effectiveness ratios.

3. *Wholly stochastic analysis* where both costs and effects are determined from data sampled from the same patients in a study, either RCT or observational. In this situation, formal statistical tests can be performed on observed differences in costs and effects. Sensitivity analysis may still be useful for assessing external validity of findings.

2.7.2 Efficiency of Technologies Within Intensive Care: The Evidence

This section examines the published evidence of efficiency of technologies used within intensive care. The quantity and quality of evidence is reported, using the hierarchical grading of evidence outlined in section 2.7.1. Virtually no effectiveness studies of technologies other than drugs have been found. Intensive care medicine often uses efficacy data from the operating theatre or ward scenario.

A literature search covering 1984 to 1995 found six economic analyses of intensive care interventions. Four of these concerned drugs, three of which related to the anti-endotoxin, HA-1A. Five economic analyses were found of drugs that could be used in an intensive care setting. Table 2.4 provides a summary of these eleven economic evaluations. An assessment of the source and grade [Eddy, 1991] of clinical and economic evidence is reported. The study designs are categorised as stochastic, partially stochastic or deterministic, and the type of economic evaluation is assessed from outcome measures reported.

The majority of the studies are partially stochastic cost minimisation studies of drugs, mostly antibiotics. Although clinical data is frequently Grade I RCT data, economic data is mostly deterministic and derived from expert opinion (Grade III data). Where the studies are reported as cost effectiveness analyses, their outcomes are usually intermediate measures such as infection rate changes [Jacobs *et al*, 1987]. The quality of the economic data is poor due to use of charges instead of costs, or use of drug acquisition costs only, with no handling of resource use related to administration, monitoring or maintenance of side effects. There are also many therapeutic areas that have not been evaluated at all. Recent evaluations of drugs have concentrated on high profile, very expensive drugs such as HA-1A monoclonal antibody [Schulman *et al*, 1991; Barriere *et al*, 1992; Chalfin *et al*, 1993]. Other 'expensive' drugs such as inotropes, sedatives and plasma expanders have not been investigated so far. Resource intensive technologies include pulmonary artery catheters, haemodiafiltration and increasingly sophisticated ventilation techniques. These have had little clinical evaluation and less economic evaluation.

The reasons for using RCTs to assess effectiveness in intensive care have been discussed in section 2.7.1. There are, however, many barriers to RCTs in intensive care, real and perceived. Due to the critical

nature of intensive care, it is sometimes difficult to obtain ethical approval or patient consent. If RCTs are done, the patient groups tend to be either homogeneous but too small for statistical inference, or large but too heterogeneous to be of use. Many unevaluated technologies in intensive care are so firmly rooted in routine practice that there would be a lot of resistance to evaluating them through an RCT. However, there are drawbacks to using economic evidence from RCTs. It reflects the practice within the trial only, such that the practice patterns may not reflect actual clinical practice, reducing external validity. Also, there is likely to be resource use associated with running the trial, such as extra monitoring tests, that need to be identified. Finally, RCTs measure efficacy in a rigorously selected patient group, rather than effectiveness in clinical practice. The resource use associated with using the same intervention in practice in a less rigorously selected population is likely to be different from the trial environment [Drummond *et al*, 1991]. The gold standard for economic evaluation is often considered to be attachment to an RCT. In intensive care, this may mean that economic evaluation of some interventions would never be done. Calling for good effectiveness data, Sheldon *et al* [1995] dismiss economic evaluation in technologies where 'evidence for effectiveness is so lacking that issues of cost effectiveness are irrelevant'. Issues of cost effectiveness in resource intensive areas such as intensive care are never irrelevant. They are simply more difficult to resolve due to lack of good effectiveness data. Sheldon *et al* [1995] also state that 'economists are too ready to carry out economic analysis on the basis of inadequate evidence about effectiveness'. In areas such as intensive care, there is very little adequate evidence, so the data available must be utilised, with explicit discussion of any shortcomings. For the economic evaluation of intensive care to progress, alternative methods of evaluation to RCTs are needed, or there may be no economic evaluation at all.

Table 2.4 Quality of Published Economic Evaluation Applicable to Intensive Care

Author	Technology under assessment	Source and grade of clinical data[1]	Source and grade of economic data[1]	Economic analysis outcome measure	Study design[2]
Moore *et al* [1986] US	Cefotaxime vs nafcillin & tobramycin for serious infection[3]	Prospective double blind RCT (Grade I)	Prospective bottom up hospital billing (Grade 1)	Cost avoided (infection rate did not differ between alternatives)	Stochastic CMA
Jacobs *et al* [1987] US	Cefoperazone in hospital acquired infection[3]	Retrospective randomised case-control study (Grade II-2)[4]	Retrospective bottom up hospital billing (Grade II-2)[4]	Cost avoided (infection rate assumed not to differ between alternatives)	Partially stochastic CMA
Buxton *et al* [1991] UK	Fluconazole vs amphotericin in cryptococcal meningitis[3]	Prospective RCT (Grade I)	Retrospective bottom up costs attached to resource use determined by expert panel (Grade III)	Cost avoided (success rate equivalent between alternatives)	Partially stochastic CMA
Schulman *et al* [1991] UK	HA-1A monoclonal antibody for treatment of gram-negative sepsis[5]	Prospective double blind RCT (Grade I)	Retrospective top down charges per bed day[6] and acquisition costs of HA-1A (Grade III)	Cost per additional survivor	Partially stochastic CEA

Table 2.4 (cont.)

Author	Technology under assessment	Source and grade of clinical data[1]	Source and grade of economic data[1]	Economic analysis outcome measure	Study design[2]
Barriere *et al* [1992] US	HA-1A monoclonal antibody for treatment of gram-negative sepsis[5]	Prospective double blind RCT of HA-1A (Grade I)	Retrospective bottom up hospital billing of sepsis patients (Grade II-3)[4]	Cost per life year saved (using estimated extra survival for age groups)	Partially stochastic CEA
Malek *et al* [1992] UK	Ceftazidime vs gentamicin combinations in severe infection[3]	Retrospective case-control observational study (Grade II-2)	Retrospective bottom up costs attached to bottom up resource use (Grade II-2)	Cost avoided (success rate assumed equivalent between alternatives)	Partially stochastic CMA
Chalfin *et al* [1993] US	HA-1A vs E5 antibody for treatment of gram-negative sepsis[5]	Separate prospective RCTs for each drug (Grade I trials)[7]	Retrospective bottom up hospital billing of sepsis patients (Grade II-3) and drug acquisition costs.	Cost per survivor	Deterministic CMA
Niebuhr *et al* [1993] Germany	Ceftriaxone vs cefotaxime for pneumonia[3]	Prospective blind RCT (Grade I)	Retrospective bottom up costs attached to predicted resource use (Grade III)	Cost avoided (success rate equivalent between alternatives)	Partially stochastic CMA

Table 2.4 (cont.)

Author	Technology under assessment	Source and grade of clinical data[1]	Source and grade of economic data[1]	Economic analysis outcome measure	Study design[2]
DePew *et al* [1994] US	Closed vs open endotracheal suctioning in ventilated patients[5]	No clinical parameters	Retrospective bottom up costs of predicted resource use (Grade III)	Cost avoided	Deterministic partial cost analysis
Holt *et al* [1994] Australia	Mask continuous positive airway pressure vs ventilation[5]	Prospective non-randomised trial (Grade II-1)	Prospective costs of bottom up resource use case-control group (Grade II-3)	Cost avoided (success rate assumed equivalent between alternatives)	Partially stochastic CMA
Paladino *et al* [1994] US	Cefmenoxime dual individualisation[8] vs standard dosing in treatment of pneumonia[5]	Separate prospective RCTs for each method (Grade I trials)[7]	Prospective bottom up hospital billing (Grade I trials)[7]	Cost per hospital antibiotic day avoided	Deterministic CEA

[1] Eddy's grades of evidence (Eddy [1991])

[2] O'Brien's economic analysis classification [O'Brien *et al,* 1994].

[3] Study carried out in hospital, not on ICU, but therapy likely to be used in ICU.

[4] Cases selected randomly, controls matched by DRG.

[5] Study carried out in ICU

[6] Changes in length of stay estimated and modelled by authors

[7] Comparison of two drugs in separate trials precludes determination of stochastic effect size differences, so necessarily deterministic.

[8] Dual individualisation refers to use of therapeutic drug monitoring to achieve optimal blood levels of drug on an individual patient basis.

2.8 IMPLICATIONS FOR ECONOMIC EVALUATION IN INTENSIVE CARE

Given the scarcity of resources, the high cost of intensive care and the doubts surrounding benefit, economic evaluation of intensive care medicine is becoming more of an imperative. This review has examined the economics of intensive care medicine and identified the issues that require most attention and empirical investigation.

The objectives of intensive care medicine have been defined in terms of both clinical effectiveness and economic efficiency in section 2.2. The importance of both allocative and technical efficiency is demonstrated. In section 2.3, a comparison of UK and US intensive care provision shows that the provision of a service within a health care system is strongly affected by the framework of that system. This needs to be considered when comparing UK intensive care provision with that from other countries. This review cannot make definitive conclusions about the allocative efficiency of intensive care due to lack of evidence either way. This is, in part, due to the lack of evidence about technical efficiency in intensive care and competing interventions. The need for information about the technical efficiency of intensive care is also demonstrated in section 2.4. The ICU patient population is large and diverse. It is essential that only patients likely to benefit are admitted to ICU. In section 2.5, the problems associated with identifying these patients is discussed. The cost of the intensive care process has been examined in some detail in section 2.6. The discrepancies between what is required for economic evaluation and what is available from published evidence are clearly shown. This discrepancy extends through all aspects of costing methodology. The major problems with cost evidence reported are the widespread use of charges instead of costs and the lack of explicit reporting of sources and components of costs. Theoretical and empirical problems associated with assessment of the impact of intensive care have been identified in section 2.7.

Again, there is a discrepancy between what is required and what is available. Information on impact of intensive care is confined to short term mortality. However, its impact on long term mortality and quality of life needs to be known for economic evaluation. A model for the impact of intensive care on quality of life has been proposed. This provides a useful point of reference when examining the specific areas where evidence for quality of life is required. The utility of intensive care has been the subject of only two studies. The measurement of utility is required for cost utility analysis, but is subject to many methodological complexities. It is difficult to attach utility values to a transient state, such as being on intensive care. There are also questions about when is most appropriate to obtain those values, or from whom. So, in conclusion, assessment of technical efficiency of intensive care is precluded by the lack of evidence on economic cost and outcomes.

This review also demonstrates that the technical efficiency of intensive care is inextricably bound up with that of its constituent technologies. Section 2.8 examines the technical efficiency of these technologies. The quality of evidence required for economic evaluation is outlined, using a published hierarchical grading system. This is used to assess the few studies found. There is clearly insufficient effectiveness and efficiency evidence about most therapeutic areas within intensive care. Reasons for this are suggested, such as difficulties associated with doing RCTs causing the lack of effectiveness evidence. The lack of efficiency evidence stems partly from this, and partly from barriers, real and perceived, to obtaining true economic cost. It proposes that, rather than using these issues as a barrier to empirical analysis, alternative methods for economic evaluation need to be developed.

Explicit consideration of resource use and consequences of high technology health care interventions is becoming an unavoidable stage

in the decision-making process because it is essential for decision makers to be able to justify their deployment. Cost effectiveness decisions should not be taken on an individual patient basis, but when unit policies are being formulated. This is particularly relevant in sensitive areas, like intensive care, where making cost effectiveness decisions on an individual patient basis would be perceived to be insensitive. The role of economic evaluation is to aid the decision making process, not to replace it. However, these decisions need to be based on accurate, reliable and generalisable effectiveness and cost effectiveness evidence. This review has demonstrated that intensive care is not able to accurately account for its resource use or measure its impact on health outcomes. This is equally true of technologies used within intensive care. This review proposes that both effectiveness and efficiency evidence are urgently required to better inform policy-makers about the net benefit of intensive care.

Chapter 3: The Clinical and Economic Impact of Prevention of ICU-Acquired Pneumonia with SDD

3.1 INTRODUCTION

This chapter specifically examines the clinical and economic impact of using selective decontamination of the digestive tract (SDD) to prevent ICU-acquired pneumonia. The first half of this review examines the clinical and economic implications of ICU-acquired pneumonia, a form of nosocomial infection. A *nosocomial* infection is one that is not present or incubating on time of admission to hospital. Section 3.2 describes the pathogenesis, diagnosis and epidemiology of ICU-acquired pneumonia. For health care providers, costs of ICU-acquired pneumonia derive from its diagnosis and treatment, the prolonging of hospitalization and handling of any long term morbidity. Section 3.3 describes the economic impact of ICU-acquired pneumonia, using published evidence. Nosocomial pneumonia is considered the leading cause of, or contributor to death, from nosocomial infection [Gross, 1980]. In addition to raised mortality, nosocomial pneumonia may have effects on short and long term morbidity. Section 3.4, therefore, presents the available evidence to support this.

The clinical and economic consequences of ICU-acquired pneumonia has prompted many recommendations for infection control [Haley *et al*, 1985; Daschner *et al*, 1985]. One of the more recent is SDD. SDD is very resource intensive, and its impact on patient outcome is equivocal. To date, no economic evaluation of SDD has been carried out. The second part of this review examines the evidence for the impact that SDD has on ICU-acquired pneumonia. Section 3.5 outlines the theoretical basis of SDD and evidence for efficacy is presented in section 3.6. The large body of efficacy data has given rise to many

reviews. The added information gained from these is assessed in section 3.7. The economic implications of SDD are examined in section 3.8, and the quality of published economic evidence is discussed. The implications of the evidence covered by this review for the economic evaluation of SDD are discussed in section 3.9.

3.2 CLINICAL ISSUES IN ICU-ACQUIRED PNEUMONIA

3.2.1 Pathogenesis of Nosocomial and ICU-Acquired Pneumonia

Pneumonias are defined by their causative organism and the origin of the organism (*nosocomial* or *community-acquired*). *Exogenous* infections are caused by organisms from outside the patient, such as a pneumonia caused by *Pseudomonas aeruginosa* from a contaminated humidifier. *Endogenous* infections are caused by bacteria living in the patient. The commonest causative organisms of nosocomial pneumonia are endogenous aerobic gram-negative bacilli (*Escherichia coli, Klebsiella sp., Proteus sp., Enterobacter sp., Pseudomonas sp.*, [Craven *et al*, 1992]). These bacteria inhabit the oropharynx, stomach and distal intestinal system. The principal mechanisms responsible for introduction of infection into the lungs are use of respiratory therapy or antibiotics, presence of endotracheal and nasogastric tubes, and cross infection. Development of pneumonia is dependent on the virulence and numbers of these bacteria aspirated into the lung and the ability of the host defences to protect against infection.

3.2.2 Diagnosis of ICU-Acquired Pneumonia

On suspicion of ICU-acquired pneumonia in the critically ill patient, it is essential to rapidly identify presence of infection and select appropriate

antibiotic therapy. Due to unavoidable delays in obtaining microbiological cultures, conventional criteria for diagnosis use the clinical signs of new or progressing pulmonary infiltrates, fever, leukocytosis and purulent tracheal secretions. The degree of precision of diagnosis of nosocomial pneumonia in general is the poorest of all major infections. Meers *et al* [1981] reported that in only 25% cases was a positive culture recorded. Up to 75% of pneumonias are clinically diagnosed in the absence of positive cultures, more than for any other infection [Meers *et al*, 1981]. Even when positive microbiological cultures are obtained, the results have to be used with caution. It is extremely difficult to obtain sputum or tracheal aspirate samples that are not contaminated by gastric fluids on extraction. So, most patients with fever and pulmonary infiltrates tend to be treated according to clinical diagnosis and cultures of tracheal aspirates.

3.2.3 The Epidemiology of Nosocomial and ICU-Acquired Pneumonia

Patients in hospital are recognised to be at higher risk of infection than their counterparts in the general population. Nosocomial infection rates vary widely, depending upon the presence of risk factors and the efficacy of local infection control programs [Haley, 1986]. Epidemiological evidence from the UK reports a 19.1% infection prevalence rate in hospitals, half (9.2%) being nosocomial [Meers *et al*, 1981]. The incidence of nosocomial infection is higher on ICUs than in the rest of the hospital. Patients admitted to ICUs represent 5 to 10% of all hospital patients in the UK, but they can account for 25% of nosocomial infections [Trilla, 1994]. The most common nosocomial infections among ICU patients are pneumonia (65%), urinary tract infection (17%) and bacteraemia (12%) [Vincent *et al*, 1995]. Reported ICU-acquired pneumonia prevalence rates vary widely in the literature, ranging from 15.5% [Daschner *et al*, 1985] to 60% [Kerver *et al*,

1987]. ICU-acquired pneumonia is considered the most significant infection on ICUs not only because of its high prevalence but also because of the morbidity and mortality this implies, and subsequent impact on resource use.

Factors increasing the likelihood of ICU-acquired pneumonia have been investigated. Joshi *et al* [1992] reported that ICU admissions have a base risk of 1 in 40 (2.5%) of developing ICU-acquired pneumonia. When certain factors are present, this risk increases as illustrated in Table 3.1. Most commonly reported significant patient-derived factors are existence of chronic obstructive airways disease, thoracoabdominal surgery and depressed consciousness. Significant unit-derived factors are most commonly reported are ventilation status, prior use of antibiotics and bronchoscopy [Vincent *et al*, 1995].

Table 3.1 Absolute Risk Factors for ICU-Acquired Pneumonia (Joshi *et al*, 1992).

Risk factor	Odds Ratio for acquiring pneumonia	95% CI	Absolute risk/%
Ultimately fatal disease	2.79	0.90-8.61†	7
Rapidly fatal disease	3.89	0.92-16.40†	9
Thoracoabdominal surgery	4.34	1.43-13.14‡	11
Nasogastric tube	6.48	2.12-19.82‖	16
Recent bronchoscopy	2.95	1.02-8.52†	7

† $p<0.05$; ‡ $p<0.01$; ‖ $p<0.001$

3.3 THE COST OF ICU-ACQUIRED PNEUMONIA

It has been estimated that nosocomial infections in England increase length of hospital stay by 4 days [DHSS/PHLS Hospital Infection Control Working Group, June 1986]. Using a 5% infection rate for acute hospitals, the authors calculated a total cost of £111m to the NHS in 1986, with 950,000 lost bed days. US studies have calculated that the annual cost of diagnosing and treating nosocomial pneumonia is 1.1 billion dollars a year [Wenzel, 1989]. Between one third and one half of all cases of nosocomial pneumonia occur on the ICU and about half of these are ventilated patients [Leu *et al*, 1989]. Changes in resource use due to ICU-acquired pneumonia arise from the impact on length of ICU and hospital stay and any increase in treatment intensity. This section examines the evidence available for both sources of increased resource use.

3.3.1 Increased Length of Stay

Length of stay is the most commonly used measure of resource use attributable to nosocomial infection. A variety of methods have been used to determine length of stay associated with nosocomial infection and pneumonia. The method used can affect the resulting estimates and also the confidence with which those estimates can be used in an economic evaluation. The most robust method is multivariate analysis of differences between lengths of stay between infected and uninfected groups. This enables control of confounding variables. However, the most commonly used method is matched pairs cohort analysis. Here, confounding variables are accounted for by matching similar infected and uninfected patients. Another method is to use clinicians' judgement to assess any increased length of stay due to infection.

Table 3.2 summarises the studies that have examined the impact of ICU-acquired pneumonia on length of ICU stay. Molina *et al* [1993] used multiple regression to isolate the increase in length of ICU stay. They report the most conservative estimate of increased length of stay. All other studies used the matched pairs cohort method. Matching characteristics were age, surgery prior to admission and length of exposure to risk of infection. Molina *et al* [1993] and Fagon *et al* [1993] controlled for severity of illness. The use of matched pairs leads to the exclusion of patients that cannot be matched. Kappstein *et al* [1992] reports that these tend to be older, 'sicker' and ventilated for longer. The matched pairs method is likely to produce estimates that are much larger than the regression analysis method. This is most likely to be due to incomplete matching of patients. This leads to confounding factors that have not been sufficiently matched, such as chronic health states or severity of illness, exaggerating length of stay differences. These results suggest that ICU-acquired pneumonia would increase ICU length of stay in a British ICU. None of the studies examined is British, so only the direction of the change in length of stay, rather than the actual magnitude, can be applied to the British situation.

Table 3.2 Published Estimates of Increases in Length of ICU Stay Attributable to ICU-Acquired Pneumonia

Author	Patient group	Method	Mean length of stay/days (sd)	
			Infected	Uninfected
Craig 1984 (US)	All ICU admissions	54 matched pairs of survivors	12.0 (3.8)	4.3 (1.7)†
Kappstein 1992 (Germany)	Ventilated >24 hrs	34 matched pairs of survivors	Difference: 10.13 (21.5) NST	
Fagon 1993 (France)	Ventilated >72 hours	48 matched pairs 22 matched pairs of survivors	34 41	21 † 22 †
Molina 1993 (Spain)	ICU stay >48 hours	1. 88 matched pairs 2. 220 patients in regression analysis	17.2 (12.6) 14.2	6.8 (4.2) 9.9

† $p<0.05$

NST: no significance test done

Length of stay is used both as a measure of resource use and as a measure of morbidity. However, lengths of stay are affected by factors other than infection. There are interhospital variations in process of care, physician or hospital-related characteristics that will have an impact, as well as the socioeconomic status of the patient and presence or absence of social support systems.

3.3.2 Other Resource Use Associated with ICU-Acquired Pneumonia

Treatment intensity may be expected to change due to ICU-acquired pneumonia. This can include extra treatment, staff time, respiratory support and use of diagnostic services. To capture resource use

changes attributable to ICU-acquired pneumonia, it is necessary to collect all resource use data for a group of infected and uninfected ICU admissions in an observational study. Analytical methods can then be used to identify differences in resource use attributable to infection. This data is rarely routinely recorded, requiring commitment of resources to a study.

Very few studies were found that investigated increases in resource use due to ICU-acquired pneumonia. SDD trials report increased use of antibiotics in patients who acquire pneumonia. This is discussed in more detail in Chapter Four. Other drugs, disposables and disinfectants used as a consequence of ICU infections have been reported in a Belgian study by de Clerq [1983]. This study is also reported in more depth in Chapter Four. Coello *et al* [1993] reported significantly higher utilization of microbiology ($p<0.0001$), haematology ($p<0.001$), chemical pathology ($p<0.001$) and radiology ($p<0.007$) in infected hospital patients in a British district general hospital. No published evidence to this effect was found in ICU-acquired pneumonia. No other evidence has been found on the impact of ICU-acquired pneumonia on ICU resource use in Britain.

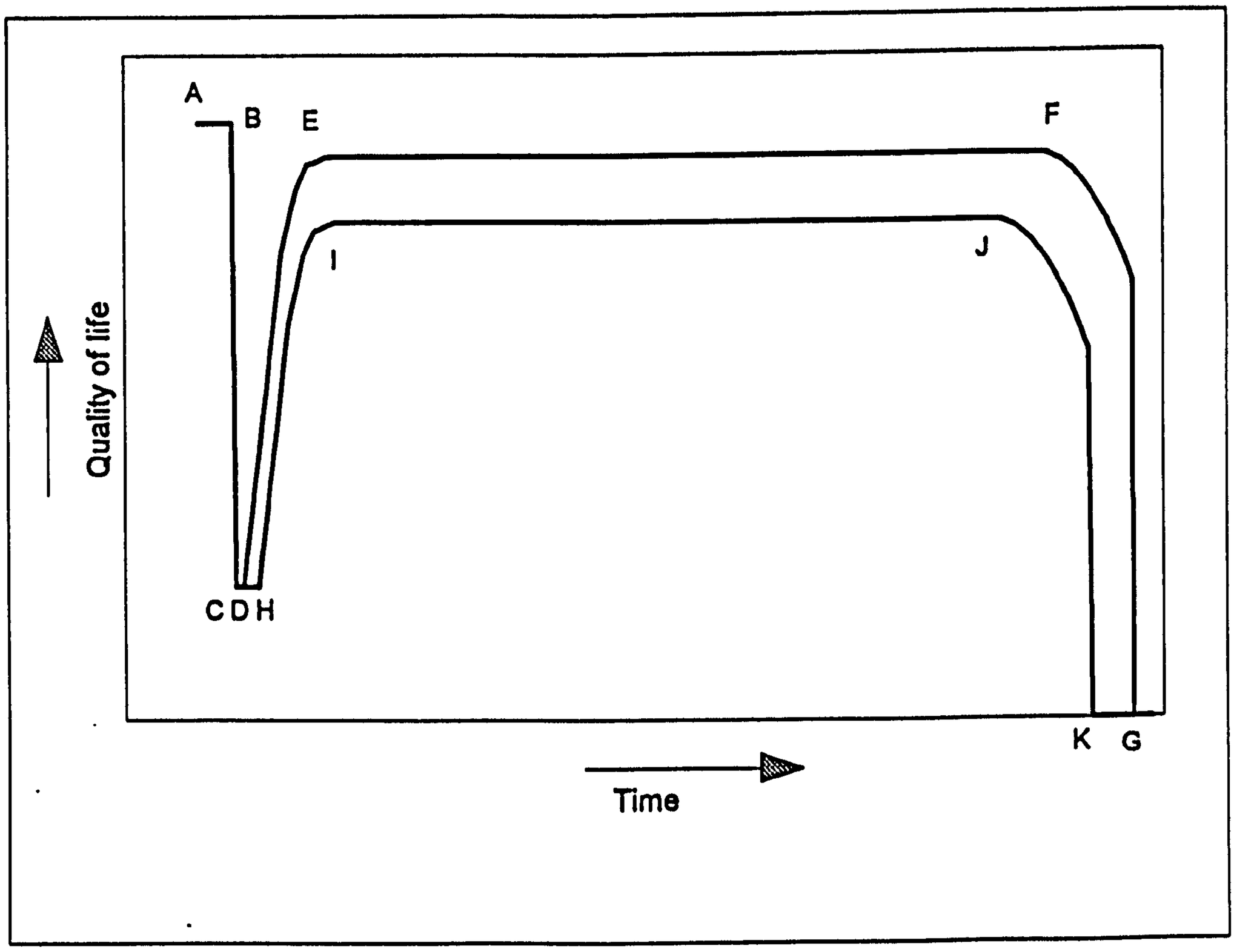
3.4 THE CONSEQUENCES OF ICU-ACQUIRED INFECTION AND PNEUMONIA

The ideal endpoint for economic assessment of a clinical intervention is an overall measure of benefit to the patient which takes account of all effects of treatment, whether adverse or beneficial, on the long term morbidity and mortality of the patient.

The overall impact of an intensive care admission on the QoL of an individual has been discussed in Chapter Two. Figure 2.1 charted the

proposed course of an ICU admission's QoL. If an individual on ICU acquires a pneumonia, this QoL profile may be affected. The first issue is that pneumonia may increase the risk of mortality whilst on ICU or in hospital, thus losing all subsequent QoL. In Figure 3.1, line ABCHIJK depicts the QoL profile of an individual who acquires pneumonia whilst on ICU. This can be compared with line ABCDEFG which depicts the QoL of a patient who does not acquire pneumonia. If the patient survives the episode, their ICU length of stay (CH) may be lengthened, increasing the period of time in a poor QoL state. Hospital length of stay may be increased and the length of time to full recovery may be increased (HI), as the patient has to recover from pneumonia as well as their original problem. The long lasting effects of the pneumonia may leave long term effects, so that the individual is never able to attain their pre-ICU QoL (IJ). There may also be an adverse effect on life expectancy, so the individual dies earlier (JK). The impact of ICU pneumonia on QoL is therefore represented by the area bound by lines ABCDEFG and ABCHIJK in Figure 3.1. To estimate this difference, evidence on the impact of ICU-acquired pneumonia on the recovery period, post-ICU QoL and life expectancy is required.

Figure 3.1 Hypothetical Model of Impact of ICU and ICU-Acquired Pneumonia on Quality of Life



ABCDEFG: ICU patient who does not acquire pneumonia whilst on ICU

ABCHIJK: ICU patient who does acquire pneumonia whilst on ICU

The remainder of this section examines what evidence is available on the impact of ICU-acquired pneumonia on morbidity and mortality.

3.4.1 Evidence for Morbidity Associated with ICU-Acquired Infection and Pneumonia

No evidence was found on the impact of nosocomial infection or pneumonia on patient morbidity, physical or psychological, short or long term. Davey *et al* [1991] note that most studies use surrogate variables, such as length of stay, as outcome measures, implicitly assuming that control of these proxy measures will result in benefit to the patient. Epidemiological studies use increased length of stay as a proxy variable for morbidity, even though patients who are most severely ill could die earlier [Leu *et al*, 1989].

3.4.2 Evidence for Mortality Associated with ICU-Acquired Infection and Pneumonia

Nosocomial infection is the leading cause of death in the US after heart disease, cancer and stroke [White, 1993]. 55.1% deaths from nosocomial infection in the US in 1988 were attributed to nosocomial pneumonia, whereas nosocomial pneumonia constitutes only 10.5% of all nosocomial infections. This disproportionate share of mortality implies that pneumonia is the most lethal nosocomial infection [Haley *et al*, 1985]. The most recent hospital infection prevalence study in the UK does not report any mortality parameters [Meers *et al*, 1981].

Stevens [1974] report hospital mortality rates of 50% in ICU patients who have nosocomial pneumonia, and 3.5% in patients who do not. Nosocomial pneumonia rates and hospital mortality from nosocomial pneumonia are highest in ventilated ICU patients. Craven *et al* [1992] report a crude mortality of 25% in non-infected ventilated patients and 55% in infected patients. A French matched cohort study by Fagon *et al* [1993] reports a crude mortality of 54.2% in patients with

pneumonia, compared with 27.1% in patients without. The authors infer from this that pneumonia-attributable mortality is 27.1%. However, it is wrong to assume that the difference between infected and uninfected mortality rates is all attributable to infection. This is because infection in ICU is considered to be, partly, a consequence of critical illness. Severely ill patients are more likely to develop nosocomial pneumonia and more likely to die from their underlying condition. Infection may or may not be a contributory factor. Logistic regression analysis by Craven *et al* [1986] identified factors which independently influence mortality. ICU-acquired pneumonia was a significant risk factor for mortality in individual analysis ($p = 0.02$) but in multiple regression analysis it did not reach significance. The most recent meta-analysis of trials of SDD [1993] is the only study to demonstrate an independently significant link between ICU-acquired pneumonia in ICU and mortality ($p = 0.003$).

No published evidence was found on the impact of ICU-acquired pneumonia on long term mortality.

3.5 THE THEORETICAL BASIS OF SDD

This review has suggested, so far, that ICU-acquired pneumonia may have serious clinical and economic consequences, many of which have not been adequately quantified. However, reduction of ICU-acquired pneumonia incidence is widely considered to be a desirable aim. Conventional infection control measures in ICUs are aimed primarily at stemming cross infections. SDD, in contrast, aims to stem self-infection, by avoiding gastric and oropharyngeal bacterial overgrowth.

In SDD, non-absorbable antibiotics are employed to eliminate the gram negative aerobic bacilli (GNAB) and yeasts in the gut that cause most nosocomial infections. ICU-acquired pneumonias are prevented by decreasing the probability of inhaling infected stomach contents. Eradication of GNABs in the lower gut decreases the amounts of GNAB-derived endotoxins that are absorbed into the bloodstream and lead to sepsis. Tobramycin or gentamicin is used, being active against GNABs, also having some activity against gram positive Staphylococcus aureus. Polymixin B or polymixin E (colistin) is used for its broad activity against GNAB. Amphotericin or nystatin is used to prevent fungal growth. The decontamination is selective because the normally predominant anaerobic bacteria in the lower gut are preserved to prevent overgrowth of resistant bacteria. ICU SDD therapy regimes consist of enteral preparations of these antibiotics as a paste applied locally to the oropharyngeal mucosa and a suspension given orally. For the first three to four days, intravenous cefotaxime is used to cover the initial period when SDD is only partially established. Drug prophylaxis is accompanied by intensive microbiological surveillance. This determines the degree of infection present on ICU admission, the efficacy of SDD in reducing ICU acquired infection rates and the emergence of resistant bacterial strains [Stoutenbeek *et al*, 1984].

3.6 EFFICACY OF SDD: A DISCUSSION OF THE EVIDENCE

SDD for critically ill patients was first propounded by Dutch researchers Stoutenbeek *et al* in 1984. They reported decreases in pneumonias, urinary tract infections, septicaemia and wound infections in ventilated patients expected to require more than five days of intensive care. A literature search was carried out from 1982 to 1994. Initial sources were Medline and Index Medicus. Unpublished work detailed in the

SDD-Trialists' Meta-analysis [1993] was obtained from the co-ordinator, R. van Saene. This search produced 37 clinical trials, four meta-analyses, 10 review articles, 25 letters and four editorials. Appendix 3.1 summarises year of publication, country of origin, design of study and type of SDD used. Of the 37 trials covered by this review, 24 are randomised controlled trials. The remaining trials are historically controlled, have consecutive control and/or contemporaneous control groups. With this method other infection control practices are more likely to be affected during the periods of consecutive control as the staff may change their practice.

3.6.1 The SDD Regimen

This section summarises the SDD regimens reported in the literature. The regimen consists of prophylactic drugs and microbiological surveillance. Variation in the regimen can stem from use of different drugs, length of treatment and intensity of surveillance. The regimens used are detailed in Appendix 3.1. 25 trials used the recommended regimen of polymixin E, tobramycin and amphotericin (PTA). Some trials substitute alternatives because of supply difficulties. These alternatives are not expected to have an effect on overall efficacy. An alternative used that would be expected to have an effect on efficacy is erythromycin [De Champs *et al,* 1993].

22 trials used intravenous therapy, 17 using cefotaxime, the remainder using ceftazidime, ceftriaxone, cephradine, cefuroxime, ofloxacin and trimethoprim. 17 trials used SDD for the entire length of ICU stay. Surveillance was reported as carried out on admission and then two to three times a week. Most common cultures taken were oropharyngeal, rectal, sputum, urine and gastric aspirate.

3.6.2 The Patients

The studies range in size from 24 patients [Fox *et al*, 1991] to 502 [Nardi *et al*, 1993]. The total number of patients investigated in the 37 trials is 5302. All studies outlined patient inclusion criteria clearly (Appendix 3.2). Most studies used SDD in patients considered to be 'high risk' from ICU-acquired pneumonia, that is, ventilated surgical patients anticipated to have a long ICU stay. Studies reported their patient groups consisting of 0 to 80% medical patients. A variety of surgical groups (vascular, cardiac, abdominal and neurosurgery) are reported, as well as trauma patients. However, the definitions of these groups and reasons for admission for these patients are not uniform between trials, limiting comparison.

Appendix 3.3 details the ages and severity of illness of the patients. Apart from the paediatric study [Zobel *et al*, 1991], studies reported mean ages of between 45 and 60. Ten studies did not report the severity of illness of their patients. Of those that did, fifteen used APACHE II. Use of a range of severity of illness scores makes direct comparison between studies more complex. Mean APACHE II scores range from 7 [Martinez-Pelluz *et al*, 1993] to 23.4 [Aerdts, 1989]. Aerdts [1989] and Blair *et al* [1991] stratified their randomisation by APACHE II score to investigate whether SDD was more effective for a particular APACHE II score band.

3.6.3 Clinical Outcome Measures in SDD Trials

Ideal outcome measures would include a measure of the incremental effect of SDD on the morbidity and mortality of the patient. However, the only outcome measures reported are reductions in infection rates and ICU mortality.

3.6.3.1 Reduction in Pneumonia Rates

The primary clinical effectiveness measure used is the reduction in infection rate and pneumonia rates. Appendix 3.4 details reductions in infection rates and their statistical significance. SDD is shown to reduce total infection rates on ICU, reducing bloodstream infections and pneumonias. The largest component of this reduction is the reduction in pneumonia rate and is the measure uniformly reported by trials. In all studies except Brun-Buisson *et al* [1989], Hammond *et al* [1990], Fox *et al* [1991] and Gastinne *et al* [1992] pneumonia rates are significantly decreased from approximately 40 to 50% in controls to 10 to 20% in SDD-treated patients. Stoutenbeek *et al* [1992] attributed the lack of efficacy by Brun-Buisson to a lower dose of polymixin E. The authors themselves attribute the lack of efficacy partly to the high proportion of medical patients (79%). Hammond *et al* [1990] and Gastinne *et al* [1992] also had a very high proportion of medical patients (62% and 72% respectively). Fox *et al* [1991] may not have produced a significant decrease due to the small size of the trial (27 patients).

Researchers attempted to identify patient groups in which SDD was most effective. Appendix 3.5 details subgroup analysis of pneumonia rate reduction. Godard *et al* [1990] investigated pneumonia rate decreases in trauma, surgical and medical patients, finding no significant difference. Blair *et al* [1991] reported a significant decrease in numbers of infected patients in the APACHE II score band 10-19 ($p=0.03$). Hammond *et al* [1992] also reported a significant decrease in number of infected patients in the APACHE II score band 17-23 ($p<0.01$), but no significant decrease in trauma patients. Verhaegen [1992] found no significant decreases in different APACHE II score bands.

No morbidity measures were reported by any study. Proxy measures were length of ICU stay (discussed in section 3.8) and length of

intubation. Fifteen studies reported length of stay, thirteen reporting no decrease (Appendix 3.5). A significant decrease from 20 to 17 days was reported by Garcia *et al* [1993] ($p<0.007$) and from 13 to 9.3 days reported by Suter *et al* [1993] ($p=0.044$).

3.6.3.2 Mortality Effects of SDD

Appendix 3.6 details the mortality reduction reported by the studies. All studies apart from Nardi *et al* [1993] reported ICU mortality. Five studies reported hospital mortality. Only three studies demonstrated a significant decrease in mortality. Rocha's study [1992] contained 79% trauma patients, all of whom were ventilated and had ICU lengths of stay of more than 5 days. Ulrich *et al* [1989] included 70% trauma and surgical patients all with ICU stays of more than 5 days. Fox *et al* [1991] only used long stay cardiac surgery patients. However, other studies with a high proportion of high risk patients [Blair *et al,* 1991; Pugin *et al,* 1991; Korinek *et al,* 1993; and Verhaegen, 1992] did not demonstrate a mortality reduction. The lack of mortality reduction could be that patients on ICU die with pneumonia, rather than from it. This is likely to be true especially in medical patients. Alternatively, the studies were too small to detect mortality differences.

Six studies carried out sub group analysis to identify patient groups whose mortality may have been affected by SDD. Ledingham *et al* [1988] and Palomar *et al* [1991] reported significant mortality decreases in trauma patients, but Winter *et al* [1992] found no difference. Godard *et al* [1990] reported a significant decrease in patients with ICU stays of more than 7 days, but Blair *et al* [1991], Winter *et al* [1992] and Ledingham *et al* [1988] found no difference. Godard *et al* [1990] also found a reduction in patients with SAPS scores of 0 to 10. Blair *et al*

[1991] found a reduction in patients with APACHE II scores 10 to 19, whereas Jacobs *et al* [1992] found no reduction in this subgroup.

3.6.3.3 Unwanted Consequences of SDD: Emergence of Bacterial Resistance

The antibiotics used in SDD selectively eradicate GNABs, which could lead to superinfection with resistant strains of GNAB, and MRSA which is not specifically targeted as much as GNABs. The retention of normal anaerobic gut flora is intended to prevent overgrowth of these pathogens. Most of the studies examined the emergence of resistance in their study groups. Significant problems have not been reported. There have been studies examining this problem specifically. Stoutenbeek *et al* [1987] reported no increase in resistance during 30 months of SDD use. The lack of emergence of resistance is due to the high concentrations of the topical agents used. The high doses eliminate even those organisms that are partially resistant.

3.7 META-ANALYSIS OF SDD TRIALS

The large number of trials and equivocal evidence surrounding SDD's effect on mortality has given rise to four meta-analyses. Table 3.3 summarises these analyses. All studies used RCTs only. The low number of studies in the recent analysis by Kollef [1994] is because they used only English language articles accessed via Medline. This gives the analysis a twofold publication bias. This is the only study that quotes absolute risk, which is more useful than odds ratios (relative risk) for economic evaluations that use decision analysis. The two most reliable meta-analyses carried out are those by the SDD Trialists' Group [1993] and Heyland *et al* [1994]. The former is the least susceptible to

publication bias as four unpublished trials have been included. Methods used by Heyland *et al* [1994] are the most rigorous. They carried out a criterion-based systematic review to assess the method quality of the studies. The studies were given a score according to quality of method (randomisation, blinding and use of placebo), patient selection and population description, reproducible description of methods, outcome measures and diagnostic criteria. However, some scores were subjective and there was 'modest agreement between assessors' which limited the strength of inference. The drawback of this meta-analysis was the exclusion of some studies (Palomar, Cerra and Kerver) because the original papers did not distinguish between the number of infected patients and number of infections. The SDD Trialists overcame this by contacting original authors.

Table 3.3 Summary of Published Meta-Analyses

Study	No. RCTs (patients) in analysis	Relative Odds Ratios for pneumonia with SDD (95% CI)	Relative Odds Ratios for mortality with SDD (95% CI)
Vandenbroucke-Grauls *et al* [1991]	11 (1489)	0.12 (0.15-0.29)	0.90 (0.40-1.53)
SDD Trialists Collaborative Group [1993]	22 (4142)	0.37 (0.31-0.43)	0.90 (0.79-1.04)
Kollef [1994]	16 (2270)	Absolute risk Control: 21.9% SDD: 7.4%††	Absolute risk Control: 26.2% SDD: 24.3% ns
Heyland *et al* [1994]	20 (3395)	0.46 (0.39-0.56)	0.87 (0.79-0.97)

†† $p < 0.0001$

All meta-analyses reported a very significant reduction in pneumonia rates when SDD is used. A review by Loirat *et al* [1992] suggests that SDD should be directed at a previously healthy ICU population with acute moderate to severe disease and a good prognosis provided infectious complications can be avoided, such as trauma and burns patients. The meta-analyses were not able to carry out subgroup analyses to identify target patient groups due to the inconsistency of diagnosis definitions between studies.

Mortality odds ratios imply that SDD has a marginal effect on mortality. SDD only affects mortality through its reduction of pneumonia rates. Section 3.4 has discussed the difficulties in attributing mortality to pneumonia. The meta-analysis by the SDD Trialists group suggests that a trial of 2000 patients would be required to demonstrate a significant mortality reduction of 10%. The meta-analyses show an overall decrease in mortality of 10%. As the meta-analyses include more patients, this estimate does not change, but its confidence intervals become narrower.

3.8 ECONOMIC IMPACT OF SDD

Changes in resource use due to SDD arise from its implementation and its impact on pneumonia rates. This in turn has an effect on length of ICU and hospital stay and any increase in treatment intensity. This section examines the evidence reported by SDD trials for incremental resource use changes associated with SDD implementation and its effect on pneumonia rates.

Appendix 3.7 summarises resource use information available from the literature. Five trials do not report any resource use information at all, 16 trials only recording ICU length of stay. In writing to the authors of

the studies only one was able to provide any information at all on the sources of their costs (personal communication, Dr. L. Rocha, 1993). SDD is a resource intensive intervention, using costly antibiotics in preparations that have to be made in the hospital. It is time consuming to prepare and administer. Microbiological surveillance in the trials is also intensive. Only seven trials quote SDD regimen costs, in varying detail. Winter *et al* [1992], Korinek *et al* [1993] and Suter *et al* [1993] did not report the source of costs or the year from which the costs were derived. Gastinne *et al* [1992] obtained their drug costs from their pharmacy department, but did not detail the components of costs reported.

Impact of SDD on resource use associated with pneumonia was largely confined to impact on length of ICU stay. Length of stay was reported by thirty studies. Mean lengths of stay were usually over ten days, reflecting the severity of illness of the patients included in the studies. No significant difference was reported between treatment and control lengths of stay for most studies. Verhaegen [1992] reported a reduction in length of stay for the treatment group receiving ofloxacin ($p = 0.012$), but no reduction for the group receiving PTA. Verhaegen [1992] also reported that once infection is established, SDD has no independent effect on length of stay (see Chapter Four). Suter *et al* [1993] reported a reduction from 18.5 days to 12.7 days when PTA was used. Impact of pneumonia on treatment intensity was largely confined to measurement of therapeutic antibiotics. Rocha *et al* [1992] provided the most detailed cost breakdown of all the SDD trials. They used 'real costs' for staffing, pharmacy and 'sanitary material' and hospital charges for diagnostic procedures, administration, nutrition and other services (personal communication, Dr. L. Rocha, 1993). Unlike the other studies, they also related costs to outcomes to derive cost effectiveness ratios. Cost per survivor was reported to be lower in SDD

treated patients (see Appendix 3.7). This suggests that SDD was more effective at a lower cost, so is considered a *dominant* therapy.

The many reviews and editorials devoted to SDD have used its high cost as a reason for recommending against its use [Atkinson *et al*, 1993]. Reviewers sympathetic to SDD recommend that cost effectiveness studies are needed to justify its use [Boom *et al*, 1992; Reidy *et al*, 1990]. SDD trialists have examined the cost effectiveness of SDD. Aerdts [1989] and Verhaegen [1992] devoted thesis chapters to 'cost effectiveness analysis'. Neither author reported sources or breakdowns of costs. Also, the costs reported were not related to clinical outcome in any way.

Two reviews have examined the cost implications of SDD. The original developers of SDD derived a value for cost per survivor (Miranda *et al* [1983]) of $22326. The methods used to obtain these costs were not reported. A more recent review of the economics of SDD in ICU patients [Markowsky *et al*, 1994] summarised the cost figures reported by SDD trialists, but did not attempt to draw any economic conclusions from the primary research.

3.9 CONCLUSIONS OF THIS REVIEW AND IMPLICATIONS FOR ECONOMIC EVALUATION OF SDD

This review has demonstrated that ICU-acquired pneumonia is considered to be the nosocomial infection with the most profound effect on resource use and patient outcome. The relationship of ICU-acquired pneumonia with mortality is complex and has not been clearly quantified. The situation where patients with pneumonia ultimately die of their underlying condition, rather than the infection, complicates this relationship. It may be that impact of ICU-acquired pneumonia on the

morbidity of survivors is a more appropriate outcome measure. Adverse morbidity associated with development of ICU-acquired pneumonia has not been quantified, although it could be implied from the increased length of ICU stay of infected patients. Due to the relative shortage of ICU beds in this country, an important organisational consequence is that of beds being filled by patients with ICU-acquired pneumonia. This means that other patients requiring intensive care are not receiving this care, increasing their risk of adverse outcomes. It is therefore desirable to reduce ICU-acquired pneumonia to reduce possible morbidity and mortality of the infected patient and also that of other potential ICU patients.

The economic impact of ICU-acquired pneumonia has not been fully quantified, but the increase in intensity of intervention due to infections has significant resource implications. The nature of this resource use has not been sufficiently reported so far. The most appropriate method to determine whether increase in therapeutic intensity due to infection exists is to collect bottom-up resource use data and attach costs to that resource use. This method is resource intensive itself and the incremental benefit of carrying out such a study should be considered.

This review has examined the clinical and economic evidence associated with SDD. The existence of 37 clinical trials of an intervention, 24 of which were well designed RCTs, is unusual in the ICU setting. These trials represent a large commitment of resources to an intervention that does not attract universal support. SDD unequivocally reduces ICU-acquired pneumonia rates but has an equivocal effect on mortality. This review has demonstrated how difficult it would be to show an independently significant effect on short term mortality. Although nearly all the studies report significant decreases in pneumonia rates, authors and commentators voice their concern about the lack of reduction of mortality, the possible emergence of resistance and the

high cost of implementing the SDD regimen. Despite the lack of economic evidence from trials, reviewers argue against the use of SDD on the basis that it is not cost-effective [Loirat *et al*, 1992; Reidy *et al*, 1992]. However, no economic analysis has been carried out.

On the basis of the available evidence, this review is not able to derive any conclusions on the cost effectiveness of SDD. The relevant economic issue is whether it is more cost effective to treat ICU-acquired pneumonia as it occurs, or to reduce its rate with SDD. It may be that SDD reduces total cost as well as improving patient outcomes, in which case it becomes dominant. It may be that it improves patient outcomes at an increased cost. In this case, incremental cost/outcome ratios need to be derived. This has not, so far, been satisfactorily addressed. Economic evaluation of SDD needs to take into account the resource use and outcome effects of ICU-acquired pneumonia, and then examine the effect SDD has on them. It is suggested that conclusions on the cost effectiveness of SDD cannot be made until there has been a formal consideration of costs and benefits.

Chapter 4: A Secondary Economic Evaluation of SDD

4.1 INTRODUCTION

Chapter Three has suggested that there is a need for the economic evaluation of SDD to improve the information upon which policy decisions are made about SDD implementation. However, to date there has been no economic evaluation of SDD and it is not known how cost effective it is. The discussion in Chapter Two has outlined reasons why economic evaluations of technologies used within intensive care are not frequently undertaken.

There are two main ways to carry out economic evaluations. Prospective economic studies provide primary economic data where empirical data is collected as part of an RCT or observational study. However, prospective studies are themselves resource intensive. They can only be recommended if it is considered that a prospective study could provide information that will improve decision-making. Assessment of whether a prospective study is warranted is done by carrying out an economic evaluation using secondary sources of data, primarily published clinical and economic evidence. Published data are retrieved, usually from multiple sources, and used to derive cost/outcome ratios for the intervention. This information is already available so does not have the same resource implications as primary data. Modelling in economic evaluation can be used either as a first or last resort. As a first resort, it is used to indicate whether primary economic analysis is warranted and which specific areas of evidence are required to improve the robustness of any conclusions made. As a last resort, it is used when a primary economic analysis is not feasible. Also, if

the published evidence is considered sufficient, it may be possible to carry out an economic evaluation without recourse to a primary study.

This chapter describes a secondary economic analysis of SDD. Section 4.2 outlines the specific aims and objectives. Section 4.3 describes the methods used in the analysis. Section 4.4 reports on the use of these methods in the economic analysis of SDD. The results of this economic evaluation are discussed in section 4.5 and the implications for future economic analysis of SDD are examined in section 4.6.

4.2 AIMS AND OBJECTIVES OF ECONOMIC EVALUATION

The aim of the secondary economic analysis of SDD is to derive conclusions regarding the cost effectiveness of SDD using published clinical and economic evidence.

The specific objectives of this economic analysis are:

1. To use the available clinical and economic literature to assess the conditions, if any, under which SDD can be demonstrated to be cost effective.

2. To determine whether conclusions can be drawn on cost effectiveness of SDD on the evidence available and identify areas where more evidence is needed.

3. To comment upon the appropriateness of applying secondary economic analysis methods to answer questions of cost effectiveness in intensive care medicine in general and in SDD in particular.

4.3 METHODS OF ECONOMIC EVALUATION

This section describes the methods used in economic evaluation. The aim of economic analysis of an intervention is to determine whether, under specified conditions, it is cost effective. Economic evaluation can be considered to consist of four stages. The first stage is the derivation of the research question. In this thesis, decision analysis is used to define the research question and express the intervention as a decision-analytic pathway [Weinstein, 1980]. The second stage is to obtain economic and clinical evidence to apply to the decision-analytic model. In primary economic evaluation the data comes from primary sources. This is either a prospective study attached to an RCT or an observational study. In secondary economic evaluation, the sources of data are published evidence. Systematic review of economic and clinical data is used to find and assess information to combine with the decision-analytic model. The third stage is the combination of clinical and economic parameters within the decision model framework to derive cost/outcome ratios. This involves the analysis of the incremental effect of an intervention on overall resource use and patient outcome, compared with alternatives. In the fourth stage, the robustness of these ratios is examined using sensitivity analysis to determine how much variation in which parameters has most effect on conclusions drawn. These methods are used in the secondary economic analysis of SDD reported in this chapter. The specific methods used in the four stages are presented in the next four sections.

4.3.1 Derivation of Research Question

In this thesis, the framework of decision analysis is used to derive the research question. Decision-analytic models provide a clear and intuitive

framework within which an economic question can be developed [Weinstein, 1980]. The ideal decision-analytic model is that which most closely resembles real life situations without being prohibitively complex. The use of decision analysis enables the research question to be identified and bound within a set of explicit conditions. This requires that the intervention and any alternatives are described in terms of inputs, process and outputs. The perspective or viewpoint of the analysis is defined at this point. Evaluations may assume the viewpoint of a single provider, the NHS, the patient or society. The perspective affects which costs are included and at which points within the intervention process the evaluation begins and ends.

The input to the process is the patient group appropriate for the intervention. The intervention process begins with the decision of whether the patient is appropriate for treatment or not. The next stage is to describe all alternative treatments under consideration. A 'no treatment' option should be included if appropriate. In all alternatives, all stages of the intervention process need to be stated, including lengths of operating time, drug regimes used including doses and lengths of treatment, and any investigational or diagnostic tests routinely required.

The stages at which treatments may be altered or discontinued need to be known, as does under which criteria these occur and what, if any, alternative treatment is implemented. Probabilistic events expressed as chance nodes define the intervention process. The degree of exclusivity of the alternatives may vary. The complication rates of each alternative and their maintenance are required to assess their full economic impact.

The final component of the decision-analytic pathway is patient outcome. An ideal outcome measure provides a measure of the impact of the

treatment on quantity and quality of life. In practice, intermediate outcomes are often used as multiattribute outcome measures are methodologically complex and time-consuming to collect. The clinical effectiveness measure used determines the type of economic evaluation. If two alternatives are equally effective, they need only be differentiated by their economic impact, giving rise to cost minimisation analysis. The use of a linear, unidirectional measure of outcome to compare effectiveness, such as life years gained, gives rise to cost effectiveness analysis. When multi-attribute measures of outcome are used, which combine measures of impact in both quantity and quality of life to produce measures of utility, the evaluation is a cost utility analysis. Where benefits are expressed in monetary terms, the evaluation is a cost benefit analysis.

Once the components of the research question have been identified, they are structured in a logical and temporal sequence. This involves defining the clinical starting point, from which the sequence of events is described. The time horizon of the decision-analytic model is defined, as well as measures of patient outcome and the time at which the treatment ceases to have any more effect on outcome.

4.3.2 Acquisition of Economic and Clinical Evidence

The second stage in an economic evaluation is to obtain clinical and economic evidence required to fill the decision-analytic model. In secondary economic analysis the source is published research. It is essential that the most robust evidence is used. The quality of evidence was discussed in Chapter Two. *Robust evidence* can be considered to consist of data that have been collected using rigorously designed methods, as discussed in Chapter Two, section 2.7.1. From Eddy's grades

of evidence, the most robust source is held to be RCTs. Secondary data are preferably obtained from RCTs. However, in therapeutic areas such as intensive care, the quantity and quality of economic data available are usually far from satisfactory. Therefore, it is necessary to utilise all possible sources of data and then assess which data are appropriate for use in an economic analysis.

When there is much clinical or economic evidence, it is necessary to select the most robust data by literature review. Traditional reviews can be subject to the idiosyncratic impressions of the individual reviewer. *Systematic* review and critical appraisal of published evidence using simple guidelines provide an objective assessment of the research less prone to reviewer bias. Mulrow *et al* [1994] list the following justifications for systematic review:

1. When there are many studies on an intervention it allows synthesis of large quantities of information into 'palatable pieces for digestion'.

2. Integration of critical pieces of information provides estimates of variables and outcomes for use in economic evaluation and decision analysis.

3. It is usually quicker and less costly than embarking on a new study. It can shorten the time between medical research discoveries and clinical implementation of effective strategies.

4. Establishment of generalisability provides an interpretative context not available in any one study.

5. There is assessment of consistency of relationships and whether effects are in the same direction and of the same magnitude.

6. Explanation of inconsistencies and conflicts in data is possible.

7. There is often increased statistical power. This is particularly relevant to relatively low event rates or when small effects are being measured.

8. Increased precision of risk or effect size by narrowing of confidence intervals around point estimates.

One major objective of systematic review is to combine individual study results into pooled point estimates (with confidence ranges) of effect size. *Meta-analysis* is the formal approach to combining evidence from multiple sources to calculate point estimates and confidence intervals for parameters of interest. Meta-analysis weights reported evidence according to the number of subjects and variance of results of each study. Confidence intervals indicate the precision of the result obtained [Patel, 1988]. The studies should contain robust data and it must be certain that they are all measuring the same effect of the same intervention in the same subject group. To achieve these two aims, it is necessary to have explicit inclusion criteria. The quality of evidence available is the primary concern. Most weight should be given to studies that are least subject to bias and error, that is RCTs [Light *et al*, 1984]. Publication bias occurs when researchers and publishers are more inclined to publish studies with positive results than with negative or inconclusive results. It is possible to determine how many unpublished observations would be required to influence the significance of a meta-analysis finding. This issue is at least made explicit by meta-analysis. Meta-analysis gives more weight to larger

studies, so the impact of smaller studies is given an appropriate weight.

Another problem with comparing studies is the concern of whether treatment groups in different studies are the same in fact as well as in name. This is often difficult to determine from a published report. A related problem can be whether control groups are comparable to treatment groups, which is why RCT-derived data is preferably used. It is also essential that studies use the same units of analysis. The review should only compare those studies that use the same measures of outcome and quote confidence intervals and statistical tests.

The ideal situation exists where all clinical and economic evidence relating to an intervention are collected from the same robustly designed RCTs. Unfortunately, this situation is unlikely to occur, at the present time, in intensive care medicine, and in many other therapeutic areas. Therefore, it is necessary to use alternative sources of data. These sources may include less rigorously designed studies such as are described in Chapter Two. Case-control studies, observational studies, routinely collected data, or that collected from 'expert panels' are common alternative sources. RCT data are preferred because they are stochastic and control for bias. Precision, or lack of it can be quantified, and it is possible to draw statistical inference from the sample to the population from which the data are drawn. Data not drawn from random sampling, that is, deterministic data, do not allow this type of analysis. This issue is more relevant in the acquisition of economic data. The use of this type of data usually decreases the precision of point estimates. Sensitivity ranges have to employed, instead of statistical ranges. These are less satisfactory because of their subjectivity.

Apart from the quality of the data available, it is necessary to be able to

account for all effects on the patient and all changes in resource use. Therefore the final outcome of the patient should be assessed, not just intermediate outcomes. All resource use associated with an intervention should be identified and costed, as discussed in Chapter Two.

The ability of the model to identify specific areas where there is a lack of data is important. This information should direct priorities for further research.

4.3.3 Derivation of Incremental Cost/Outcome Ratios

The third stage in economic evaluation is to combine the clinical and economic evidence with the decision-analytic model. Clinical probabilities and resource use along each pathway are combined to derive the probabilistic cost for each pathway. The first stage is to build a base case. This combines the clinical outcome point estimates with the economic cost associated with each stage of the model. If one of the alternatives is more effective and less costly, it is termed the dominant therapy. When one alternative is more effective but requires more resources, the cost required to achieve each extra unit of outcome is calculated. If the outcome measure is single and unidirectional, this provides an incremental cost effectiveness ratio. The lower the value, the more cost effective the alternative. In cost utility analysis, the cost/outcome ratio should provide a measure of the cost to obtain one more unit of multiattribute outcome, such as QALYs. When this outcome measure is not available, the outcome measures used must be justified. If outcome measures used are only intermediate outputs, such as number of cases detected or decrease in infection rate, this must be stated.

4.3.4 Sensitivity Analysis: Indications for Use and Standard Methods

The fourth stage of economic evaluation is the assessment of the robustness of the cost/outcome ratios derived. In this situation, *robustness* refers to the sensitivity of cost/outcome ratios to uncertainties in the data or alternative methods of analysis. If the conclusions about cost effectiveness do not change when these parameters are varied, the conclusions can be considered to be robust. The robustness of conclusions is examined using *sensitivity analysis*. Sensitivity analysis has many functions when used within an economic analysis. Uncertainty in underlying assumptions, including analytical methods, weakens an analysis. The use of sensitivity analysis goes some way to quantifying the degree of uncertainty existing in an economic evaluation. It may also increase the level of uncertainty by identifying uncertainty not previously examined. The use of sensitivity analysis identifies areas where more research is required to increase robustness. Sensitivity analysis can improve the generalisability of a study. It is particularly useful when applying ranges to point estimates derived from deterministic data. As discussed earlier, clinical evidence is much more likely than economic evidence to be available as stochastic data. Economic evidence, if available at all, is often reported as deterministic data. Uncertainty surrounding the available resource use data is often very significant due to inadequacy of the point estimates. It is necessary to assess the impact of variation of these estimates. The variation examined should reflect realistic ranges of the point estimate. Studies which provide a source or explanation for the ranges used are likely to be of more use to decision makers than studies which employ an arbitrary range in their sensitivity analysis.

There is more than one way of conducting a sensitivity analysis [Briggs *et al*, 1994]. 'Simple' sensitivity analysis varies one or more parameters

across a plausible range. In 'one-way' analysis, each uncertain component is varied individually, to establish the separate effect of each on the results of the analysis. This may be sufficient if each of the uncertain components is independent of the others. 'Multi-way' simple sensitivity analysis varies two or more components at the same time. However, it becomes progressively more difficult to present the results of multi-way analyses the greater the number of components that are varied. A form of this is 'scenario analysis' which explores the implications of alternative 'states of the world', each of which affects a number of parameters in an evaluation. 'Threshold analysis' is concerned with identifying the critical value of parameters above or below which the conclusions of the study will change. Threshold analysis is useful in cost effectiveness analysis in defining points at which the therapy under investigation becomes dominant. Another method is 'analysis of extremes'. This involves comparing a base case scenario with the most pessimistic and most optimistic scenarios.

4.4 SECONDARY ECONOMIC EVALUATION OF SDD

This section reports the secondary economic evaluation of SDD. It investigates whether SDD can be demonstrated to be cost effective compared with appropriate alternatives. Using the methods described in section 4.3, the research question is defined through the design of a decision-analytic model. Clinical and economic sources of evidence are identified to provide data to apply to the model. Cost/outcome ratios are derived and their robustness is examined using sensitivity analysis.

4.4.1 Definition of Research Question

This section defines the research question and proposes a decision-analytic model to provide a framework within which to answer that research question. The clinical aim of SDD is to decrease the incidence of ICU-acquired pneumonia, as defined in Chapter Two, and its associated morbidity and mortality. The actual category of pneumonia affected is late-onset Gram-negative pneumonia only. The economic aim is that this should be carried out as efficiently as possible, that is, maximizing output for a given level of input. The research question in this analysis asks whether SDD can be shown to be cost effective. To address this question in a systematic way, it is necessary to examine the process of the intervention and represent it as a decision-analytic model. The input and the process of the intervention, its associated resource use and outcome need to be identified.

4.4.1.1 Input to the Intervention

The input to the intervention is the patient group considered appropriate for SDD therapy are those ICU admissions considered most at risk from ICU-acquired pneumonia. Therefore, the target patient group is ventilated ICU admissions, as discussed in Chapter Three.

4.4.1.2 Process of the Intervention

The next stage is to describe the process of the intervention of SDD. From the literature review reported in Chapter Three, SDD is known to consist of topical application of antibiotics (polymixin E, tobramycin and amphotericin:

'PTA') to the buccal mucosa and gastrointestinal tract in combination with an intravenous broad spectrum antibiotic (cefotaxime). Intensive microbiological monitoring is employed to assess the infective state of the patient and to monitor the emergence of resistant bacterial strains. The SDD treatment regimen is either implemented totally, or not at all. There is no intermediate alternative. The alternative to SDD is not to treat, and treat pneumonias as they occur. SDD is either used for the whole of the ICU stay or just whilst the patient is ventilated. The patient either receives SDD from the beginning of the ICU stay or does not receive it at all. The patient will not receive SDD once they return to a normal ward. SDD would not be initiated in the middle of the ICU stay. The occurrence of ICU-acquired pneumonia in patients who do and do not receive SDD will lead to therapeutic interventions which are not expected to differ between SDD-treated and non SDD-treated patients. It is necessary to identify the resource use associated with each stage of the intervention process and attach unit costs to that resource use. This economic evaluation aims to assess the long term impact of implementation of SDD. Therefore, the costs should include all fixed and variable components, as recommended in Chapter Two. This provides a total cost for the patient, which can be equated to their long run marginal cost.

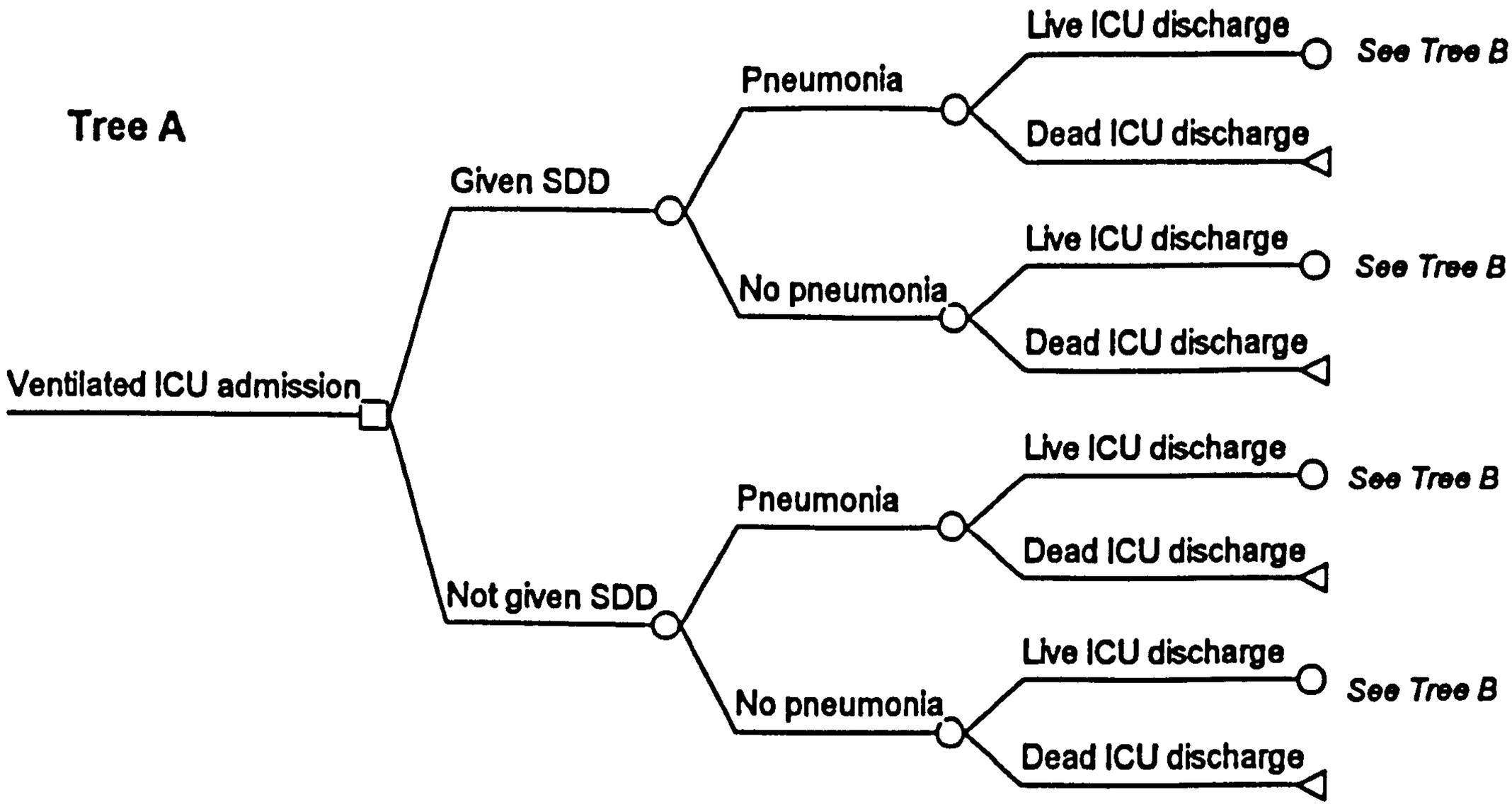
The first category of economic measures required are the impact of the SDD regimen. The second category arises from the impact of SDD on ICU-acquired pneumonia rates. Chapter Three has identified that ICU-acquired pneumonia has a significant impact on resource use. This impact occurs mainly through the increase in length of ICU stay due to an episode. There is also some evidence that treatment intensity is increased. If SDD affects ICU-acquired pneumonia incidence, it therefore affects resource use due to that pneumonia.

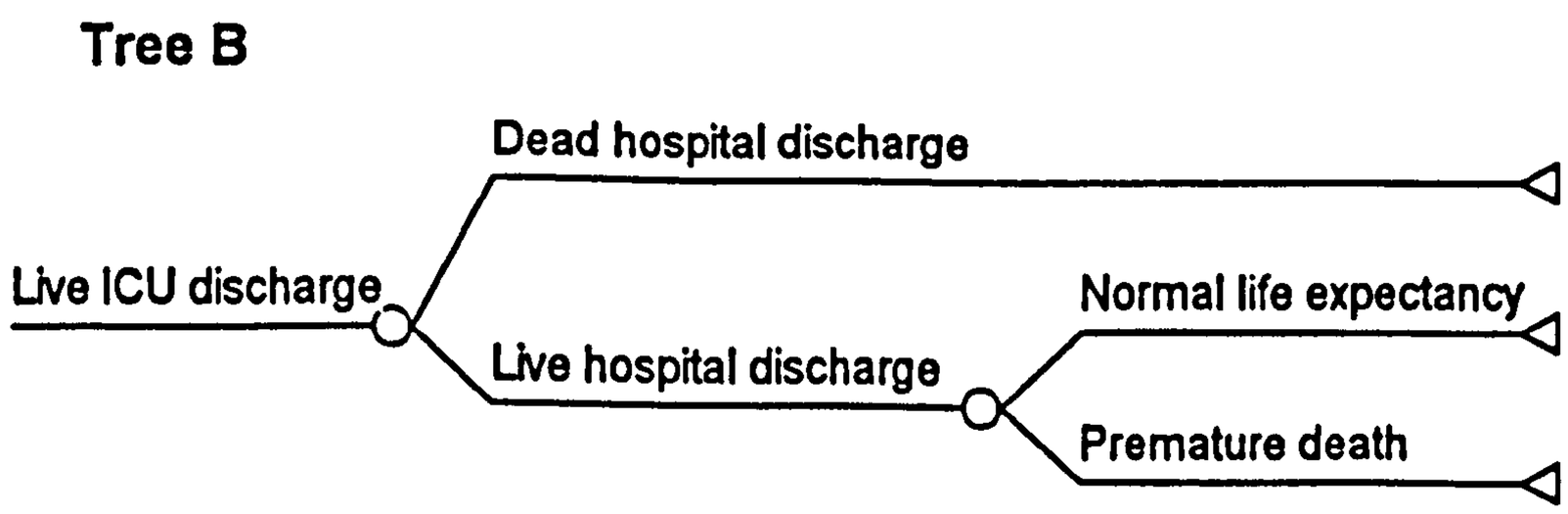
4.4.1.3 Outcome of the Intervention

The type of cost/outcome ratios derived depends upon the outcome measures used. The effect on clinical outcome of SDD is considered to be its effect on patient morbidity and mortality through its effect on ICU-acquired pneumonia incidence. If SDD is not shown to change patient outcomes, but resource use only, then it becomes a cost minimisation analysis. If there is a difference in patient outcome arising from the use of SDD, cost/benefit or cost/outcome analyses are used. Ideal patient outcome measures combine the impact of SDD on quality and quantity of patients' lives.

Once the components of the research question have been identified, they are structured into a logical and temporal sequence in a decision-analytic model. The model developed for the implementation of SDD in ventilated ICU admissions is shown in Figure 4.1. The first step is to define the starting point of the model, which in this case is the point of admission to ICU. The second step is to select a time horizon, that is, the point at which final outcomes are measured. The ideal time horizon includes the whole life span of the patient so that all possible effects of the intervention can be examined. Probabilistic events and events arising as a result of clinical decisions need to be distinguished from one another. The only decision involved in this intervention is whether to administer SDD to this group of patients, or not. All subsequent consequences are probabilistic. When a ventilated patient is admitted to ICU, he has a known risk of contracting ICU-acquired pneumonia. ICU mortality, hospital mortality or life expectancy may be affected by an episode of ICU-acquired pneumonia. SDD changes the probability of developing ICU-acquired pneumonia and, thus, any associated change in risk of mortality. This defines the chance nodes of the decision-analytic model.

Figure 4.1 Decision Tree for Use of SDD in Ventilated ICU Admissions





Only when the combined information of clinical probabilities, outcomes and economic cost are known can the decision-analytic model be used to examine the cost effectiveness of SDD. The clinical and economic evidence required for the decision-analytic model can be summarised into five categories:

1. The probability that the patient will contract ICU-acquired pneumonia with or without SDD;

2. The impact of ICU-acquired pneumonia and SDD on the short and long term mortality of the patient;

3. The impact of ICU-acquired pneumonia and SDD on the short and long term morbidity of the patient;

4. The impact of ICU acquired pneumonia and SDD on the resource use associated with the patient;

5. The unit costs associated with resource use.

The acquisition of clinical and economic evidence for these five categories is described in the next section.

4.4.2 Acquisition of Clinical Evidence

This section describes acquisition of information required by the decision analytic model by examination of the available clinical literature. The clinical evidence required for the decision-analytic model consist of the first three categories in the previous section. The ideal sources of these

categories of data are RCTs of SDD. The extent to which the evidence required can be extracted from these sources is examined. Alternative sources of evidence are used if necessary. The limitations of data drawn from these alternative sources is discussed. Any steps necessary to transform the data into a form where they can be used in the decision-analytic model for economic evaluation are reported. A summary of the clinical data obtained for use in the secondary economic evaluation is provided at the end of this section.

4.4.2.1 Derivation of Clinical Probabilities from Trials of SDD

This section examines the evidence on the effectiveness of SDD available in SDD trials. A literature search on SDD was carried out from 1982 to 1994. SDD in ICU patients was first designed in 1983 and reported in 1984 [Stoutenbeek *et al*, 1984]. The initial sources used were Medline and Index Medicus. The original designers of SDD were contacted for information on any unpublished trials. Any unpublished work detailed in the SDD-Trialists' Meta-Analysis [1993] was obtained from the co-ordinator, R.van Saene. This search produced 37 clinical trials of SDD, four meta-analyses, ten review articles, 25 letters and four editorials. One review of the economic implications of SDD was found, but no formal economic evaluation. The volume of clinical literature required that it be systematically reviewed to extract the 'best' quality evidence to be used. Inclusion criteria were designed, as discussed in section 4.2. The systematic review of the SDD literature was carried out using the following inclusion criteria:

1. *Only randomized clinical trials* (RCTs) were used, to decrease internal bias. If the test centre changed from using no SDD to SDD, in the case of

historic and consecutive controls, there may be associated implicit changes in other infection control practices as nursing and medical staff are likely to change their normal practice. This also happens in RCTs but to a lesser extent, and temporal changes in infection control practices, such as improved handwashing should be equal between the trial and control groups. Blinded trials are the ideal, but realistically have been difficult to achieve in SDD.

2. *Only trials with explicit patient inclusion and infection diagnosis criteria* were used.

3. *No trials with components in the SDD regime* significantly different from the standard PTA regimen were included, to ensure comparable antibiotic effectiveness.

4. *No trials with ICU patient groups* considered significantly different from a representative adult population were included. It was considered that their underlying pathologies would have had a significant confounding effect on infection rates, length of stay, and mortality.

5. *Only measures that were reported in more than one study were used.*

6. Any trials that duplicated data from earlier trials were excluded.

It would have been ideal to use *only British studies* because the clinical practice variation will be decreased. However, there were only seven British studies, only three of which are RCTs. Excluding use of foreign study data would have prevented use of a lot of data.

Appendix 4.1 shows which trials were excluded and for what reasons.

Most trials were excluded on the basis of one exclusion criterion, usually because the study was not an RCT.

It was expected that trials with more medical patients would have a wider range of lengths of ICU stay and also have higher mortality, due to increased influence of underlying pathology. SDD is considered to be more appropriate and more effective in surgical or trauma patients with no underlying pathology, who are nevertheless very prone to infection. To test this hypothesis, two successively more selective sub-groups of trials were derived:

1. 'Mixed ICU' Model:

In the first subgroup only trials with less than 50% medical patients were included. This subgroup has 18 trials, covering 2828 patients.

2. 'Surgery/Trauma' Model:

The most selective subgroup included only trials with 21% or fewer medical patients to produce a model with clinical measures derived mostly from surgical or trauma patients. This subgroup had 10 trials, covering 2020 patients.

Appendix 4.2 outlines which trials were included in each group. A model containing only surgery or trauma patients was investigated. Few trials reported effect sizes exclusively for trauma or surgical patients. Definitions of trauma and surgical categories varied significantly between studies. To develop a model of surgery or trauma patients only would require access to the primary trial data.

Patient group size, effect sizes and effect size variance were obtained from

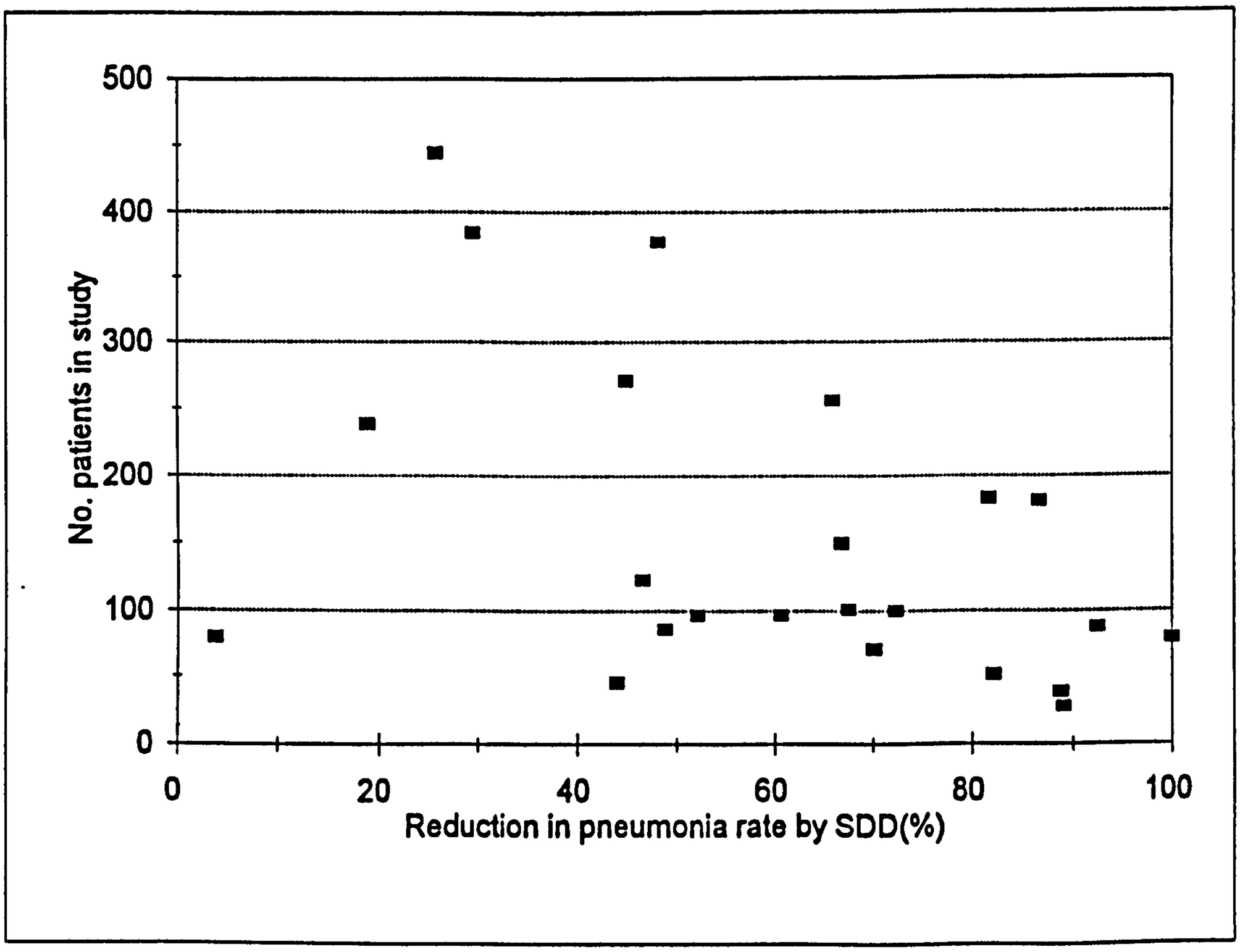
each of the included trials. The data were then pooled, using fixed effect method meta-analysis. This was carried out for each of the three groups of trials. The specific statistical methods used to derive weighted means and confidence intervals are outlined in Appendix 4.3.

4.4.2.2 Results of Systematic Review and Meta-Analysis

The above criteria were applied to the 37 trials available for systematic review. 24 trials remained for use in data extraction. Appendix 4.2 details the 24 trials that were included for meta-analysis. The 24 trials covered 3693 patients. The only clinical effectiveness parameters measured by these trials are reductions in pneumonia rates and ICU mortality. *No evidence was reported on the impact of SDD on long term mortality, or any morbidity measures.* Alternative sources had to be used, and are reported in the next section.

All the trials included were RCTs so it can be assumed that the data from them are robust. However, the presence of publication bias is demonstrated by the plot of effect size against sample size in Figure 4.2. This shows that the larger effect size is reported by small studies. When the data from these trials are pooled, the contribution from each trial is weighted by its size and reported variance. This means that the larger studies with smaller variances would have the greatest impact on pooled effect size, minimizing the effect of publication bias.

Figure 4.2 Plot of Study Sample Size Against Pneumonia Rate Reduction by SDD to Assess Publication Bias



The pooling of these trials provided weighted effect sizes for impact of SDD on ICU-acquired pneumonia rates and ICU mortality. These pooled values were derived for each of the three specified groups of trials. The clinical evidence obtained from the published literature, as appropriate for the three defined subsets of trials is summarized in Tables 4.1 and 4.3. The distribution of patient populations in each of the models is reported in Table 4.1. Weighted point estimates and confidence intervals for pneumonia rate decrease are reported in Table 4.2 and ICU mortality decrease are reported in Table 4.3.

Table 4.1 Patient Populations of Clinical Trials Groups

Parameter	All trials	Mixed ICU model	Surgery/trauma model
No. trials	24	18	10
No. patients	3693	2828	2020
% Surgical[1]	38.2 (16.1-60.3)	45.2 (18.4-72.0)	50.0 (15.5-84.5)
% Medical	31.8 (11.9-51.7)	20.5 (0.6-40.6)	12.2 (0-21.0)
% Trauma	35.1 (11.8-58.4)	38.0 (11.9-64.9)	41.4 (7.1-75.7)

[1] Weighted means (ranges in parentheses)

Table 4.1 demonstrates the variation in patient population between the models. The large confidence intervals indicate the wide variation between individual trials. The two most common patient groups included in trials for each of the three models were ventilated patients with a length of stay of

two or more days and ventilated patients with a length of stay of five or more days. Apart from the differences in the proportion of surgical to medical patients, patient inclusion criteria and SDD regimes reported for each of the three models do not differ significantly.

Effect size of SDD measured as ICU-acquired pneumonia rate reduction is reported in Table 4.2. The narrow 95% confidence intervals indicate consistency of SDD's efficacy in reducing pneumonia rates. The lack of significant differences detected between the successively more selective trial groups may indicate that SDD is not more effective in surgical and trauma patients. Alternatively, the patient groups in each trial are so heterogeneous that it effectively obscures any significant difference between trials. Also, the trials have been carried out in different countries with different clinical practice, so diagnostic definitions may also vary.

Table 4.2 Effect of SDD on Pneumonia Rates of Trials Groups

Parameter	All trials weighted means	Mixed ICU model weighted means	Surgery/trauma model weighted means
Base pneumonia rate/%[1]	29.4 (1394, 8.5-50.3%)	30.2 (1008, 5.7-34.7%)	28.8 (918, 0-59.7%)
SDD-treated pneumonia rate/%[1]	13.8 (1394, 0-35.5%)	12.7 (1008, 0-38.8%)	15.1 (918, 0-43.2%)
Effect size/%[2]	15.6 (2788, 12.7-18.5%)[3]	17.5 (2016, 14.2-20.8%)	13.7 (1836, 6.9-20.5%)

[1] Numbers in parentheses are total numbers of patients included in derivation of weighted mean, ranges.

[2] Numbers in parentheses are total numbers of patients included in derivation of weighted mean, 95% confidence intervals.

[3] Equivalent to a mean reduction in pneumonia rate of 53% (95% CI: 43 to 63% reduction).

Table 4.3 reports the effect of SDD on ICU mortality in the three trials groups. Most trials report a small, non-significant reduction in mortality. This is reflected in the small reductions in pooled mean mortality rates from control to treatment. The derived effect sizes are small and their confidence intervals indicate that they are not significant.

Table 4.3 Effect of SDD on ICU Mortality Rates of Trials Groups

Parameter	All trials weighted means	Mixed ICU model weighted means	Surgery/trauma model weighted means
Base mortality rate/%[1]	29.6 (1811, 0-51.6%)	28.1 (1409, 0-53.2%)	25.5 (1013, 0-57.7%)
SDD-treated mortality rate/%[1]	26.5 (1811, 0-48.0%)	25.0 (1409, 0-49.4%)	24.3 (1013, 0-55.9%)
Effect size/%[2]	3.1 (3622, -9.9-16.1%)[3]	3.1 (2828, -3.1-9.3%)	1.2 (2026, -3.1-5.5%)

[1] Numbers in parentheses are total numbers of patients included in derivation of weighted mean, range.

[2] Numbers in parentheses are total numbers of patients included in derivation of weighted mean, 95% confidence interval. Negative values in 95% CI indicate studies who reported an increase in mortality in SDD-treated groups.

[3] Equivalent to a reduction in mortality of 10% (range: -34 to 54%).

As this analysis has failed to show significant differences between the three models, the values from the 'All ICU' model are used in the economic analysis.

Also, SDD is not reported to increase outbreaks of resistant bacteria. No other complication rates have been reported by SDD studies. For the purposes of the decision-analytic model, it is assumed, therefore, that there are no complications associated with SDD.

4.4.2.3 Use of Alternative Sources for Clinical Evidence

The decision-analytic model requires evidence on the life expectancy and QoL of post-ICU patients and the impact of ICU-acquired pneumonia on this life expectancy and QoL. Neither has been reported in the SDD trials found. It was necessary, therefore, to utilise alternative data sources for this evidence. This section reports the evidence found on life expectancy and QoL of ICU patients and the incremental effect of ICU-acquired pneumonia.

Research into the long term survival of ICU patients is usually limited to reporting one or two year mortality. The most long term recent study is that reported by Ridley *et al* [1994]. They reported that the life expectancy of post-ICU patients is adversely affected for up to four years after ICU discharge. In the absence of any other data, most studies have used age-specific life expectancies can be obtained from reference tables. However, the assumption underlying the use of these data is that post-ICU patients have the same mortality as the general population. In their calculation of QALYs, Kerridge *et al* [1995] assume that ICU admission does have an effect on life expectancy. They assign 90% of age-specific life expectancy to ICU survivors. There is no published evidence on the incremental impact of ICU-acquired pneumonia on life-expectancy.

The decision-analytic model also requires evidence on the effect ICU admission has on QoL. This involves the measurement of QoL prior to ICU admission, QoL whilst on ICU, the length of time taken to return to a chronic QoL state and how much this state differs from QoL prior to ICU admission. The impact of ICU-acquired pneumonia and SDD on this QoL progression is also required. The impact of ICU on QoL was discussed in Chapter Two. No evidence has been found on QoL whilst on ICU, or time

taken to recover to a chronic QoL. Review of QoL literature has not revealed any studies addressing the impact of ICU-acquired pneumonia on QoL.

Consequently, there has been very little work on integration of quantity with QoL changes due to ICU admission. The only recent work is by Kerridge *et al* [1995] as discussed in Chapter Two. Discounted incremental QALYs achieved due to ICU admission is reported by diagnostic group and by APACHE II score range. These are summarised in Table 4.5. There is no published evidence that examines the impact of ICU-acquired pneumonia on QALYs gained.

Table 4.4 QALYs Gained per ICU Admission by APACHE II Score [Kerridge *et al* 1995]

APACHE II Score	QALYs achieved[1]
0-4	15.2
5-9	9.9
10-14	8.8
15-19	6.3
20-24	5.1
25-29	3.6
30-34	0.8
35+	1.2

[1] Discounted at 5%

4.4.2.4 Use of Reported Clinical Evidence in Secondary Economic Evaluation of SDD

This section examines the clinical evidence reported above for use in the secondary economic analysis of SDD. The areas examined are impact of SDD on ICU-acquired pneumonia rate, short and long term mortality, and short and long term morbidity. The robustness of the evidence is examined. Areas of uncertainty are emphasised and recommended for sensitivity analysis. Ranges for sensitivity analysis are derived from the evidence and their selection justified. The data are assessed to see whether they are in a form that can be applied to the decision-analytic model. If not, methods for altering their form are reported.

4.4.2.4.1 Impact of SDD on ICU-Acquired Pneumonia

For economic analysis, it is necessary to know the probability of acquiring ICU-acquired pneumonia, with or without SDD. The probability of a ventilated patient on an ICU acquiring pneumonia when SDD is not used is derived from the pooled value in Table 4.2 for the ICU-acquired pneumonia rate in control groups. 29.4% patients acquire pneumonia, giving a probability of 0.294. The reciprocal probability of remaining uninfected is 0.706. When SDD is used, 13.8% patients acquire pneumonia, giving a probability of 0.138. The reciprocal probability of remaining uninfected is 0.862. The reduction in pneumonia rates is 53% (95% CI 43 to 63%) in this model. Ranges for sensitivity analysis are required for reduction in pneumonia rates by SDD. SDD trials quote pneumonia rate reductions of less than 10% to 80%, although the 95% confidence intervals around the mean are much narrower. The cost/outcome ratios may be expected to be affected by variations in the effectiveness of SDD. To test for the impact

of variation of effect, the 95% confidence intervals for effectiveness (43 to 63%) are used as the sensitivity ranges. The extremes of 10 to 80% are also examined to test for the effect of larger variations.

Ranges for sensitivity analysis are also required for base pneumonia rates. SDD trials quote widely differing base pneumonia rates. If the base pneumonia rate is low, this necessarily reduces the impact of SDD, as fewer episodes of ICU-acquired pneumonia will be prevented. This can be expected to affect the cost/outcome ratios of SDD. The majority of reported pneumonia incidence rates lie between 10% and 50%. This range is used to examine the impact of variation of the base pneumonia rate on the effectiveness of SDD.

4.4.2.4.2 Impact of SDD on Short Term Mortality

For the purposes of economic evaluation, it is necessary to quantify the impact of SDD on mortality. It is also necessary to quantify the uncertainty around that impact. The probability of short term mortality of patients with or without ICU-acquired pneumonia is required for economic analysis. ICU mortality is the only short term mortality parameter reported by the SDD trials. Probability of live discharge with and without infection are required. In the absence of other evidence, it is assumed that the mortality risk from pneumonia is the same, once it has been contracted, for SDD and non-SDD treated patients. From examination of published evidence discussed in Chapter Three, it is likely that the mortality of patients who have an episode of ICU-acquired pneumonia is higher than those who do not. The SDD Trialists' Meta-Analysis [1993] demonstrates a significant independent link between ICU-acquired pneumonia and mortality ($p = 0.003$). However, the clinical trials of SDD report only mortality for SDD-treated and non-SDD

treated groups, not differentiating between infected and uninfected patients. The merged weighted mean value for SDD and non SDD treated patients is 26.7% and 29.5% respectively. These values do not reflect the probabilities for mortality of infected and uninfected patients.

There are three possible ways to derive probabilities for mortality. The first method would be to use the SDD trials and the derived meta-analysis odds ratio of 0.9. However, no base mortalities are quoted, only relative risk, which are not applicable to decision analysis. The second method is to use data from epidemiological studies of ICU-acquired pneumonia and attach their mortalities to the decision tree. The studies by Kappstein *et al* [1992], Fagon *et al* [1993] and Craven *et al* [1986] split their patients into infected and uninfected patients. However, sicker patients are intrinsically more susceptible to ICU-acquired pneumonia and often die as a consequence of their underlying disease. The infected group is intrinsically sicker and its mortality cannot be simply compared with the uninfected group. Multiple regression analysis is the most appropriate method for comparison and has not identified ICU-acquired pneumonia as an independent predictor for mortality, except in the SDD Trialists' Meta-Analysis [1993]. Epidemiological studies and SDD trials have failed to demonstrate significant changes in mortality due to pneumonia or SDD due to inappropriate groups for comparison and insufficient patients.

The third method for determining mortality probabilities is to use simple algebra to synthesise them from the data already extracted from the trial data. The proportions of infected and uninfected patients are known in the SDD and non-SDD treated patient groups where the group mortality is known. Therefore, it is possible to derive the mortalities of the infected and uninfected patients. This method is detailed in Appendix 4.5. Infected ICU mortality is calculated to be 42.3% and the uninfected mortality is

24.2%. These mortality rates can be applied to the decision-analytic model. Due to the derived nature of the values, sensitivity analysis is required to assess the impact of smaller or zero mortality increases due to ICU-acquired pneumonia.

4.4.2.4.3 Impact of SDD on Long Term Mortality

The SDD trials do not report the effect of SDD on long term mortality. No evidence on the long term mortality of ICU patients was found. Therefore, for the purposes of this analysis, the assumption made by Kerridge *et al* [1995] that the age-specific life-expectancy of ICU patients returns to 90% of the normal population is used. This assumption is used in this analysis to assess incremental cost per life year gained. Any calculations also make the assumption, in the absence of evidence to the contrary, that ICU-acquired pneumonia has no effect on long term mortality.

The majority of SDD studies report a mean age of about sixty years old, which would give a life expectancy of 19.2 years life expectancy [CSO Annual Abstract, 1991]. Assigning 90% of these years to ICU survivors is used to provide an estimate of 17.3 life years gained by ICU survivors in the model. The accuracy of this point estimate is not known because it was not derived from the population to which it is being applied. As it is a deterministic estimate, its precision is also unknown, that is, the uncertainty surrounding it is not quantified. This necessarily makes selection of ranges for sensitivity analysis ranges arbitrary. To assess the impact of the variation of life years gained on the cost per LYG ratio, the life years gained by an ICU survivor are varied from 50% of the base value (8.7 LYGs) to 150% of the base value (26.0 LYGs). These ranges reflect that SDD has been administered to adults of a wide age range (15 to 90).

4.4.2.4.4 Impact of SDD on Quality of Life and Utility

The SDD trials do not report the effect of SDD on QoL and utility. No evidence on the impact of ICU-acquired pneumonia was found. The only work found is that by Kerridge *et al* [1995] who report QALYs gained by ICU survivors. For this analysis it is assumed that SDD and ICU-acquired pneumonia affect QALYs gained via their effect on ICU mortality only. The base value for discounted QALYs (dQALYs, 5% discount rate), taken from the Kerridge values, is 6.3 per ICU survivor, as this relates to the mean APACHE scores of the majority of the SDD trials. The authors derived this value from 11.9 LYGs. The numbers of LYGs was estimated by an expert panel. The ranges for sensitivity analysis are 0.8 to 9.9 dQALYs gained (derived from 1.6 to 20.5 LYGs), to include patients with higher and lower APACHE scores.

It would be inappropriate to directly compare the LYGs from British life expectancy statistics with the dQALYs derived from Australian research data. However, it can be seen that fewer LYGs are attributed to ICU patients by Kerridge than by using the assumption of a life expectancy 90% of normal for an ICU patient. This suggests that research similar to that by Kerridge *et al* [1995] is needed to inform economic evaluation.

Table 4.5 summarises the clinical parameters required for the secondary economic evaluation of SDD. The values derived from the literature are listed, with their ranges for sensitivity analysis.

Table 4.5 Summary of Clinical Parameters, Their Associated Values and Ranges for Sensitivity Analysis

Clinical Parameter	No SDD	SDD	Incremental Effect Size due to SDD	Ranges for Sensitivity Analysis
ICU-acquired pneumonia rate/%	29.4[1]	13.8	53↓[2]	95% CI: 43-63↓ Extremes: 10-80↓
ICU Mortality/%	29.6	26.5	9.5↓	0 - 20↓
Life Expectancy per ICU survivor/LYGs	17.3	17.3	0	8.7-26.0[4]
dQALYs per ICU survivor[3]	6.3	6.3	0	0.8- 9.9[4]

[1] Base ICU-acquired pneumonia rate also varied from 10% to 50%

[2] ↓ Indicates that there is a decrease in the parameter

[3] Discount rate 5%

[4] Sensitivity analysis ranges are used to vary the parameters for both SDD and non-SDD patients.

4.4.3 Acquisition of Economic Evidence

This section examines the evidence on the incremental economic cost associated with the implementation of SDD. The two categories of economic evidence are the resource use associated with SDD implementation and treatment of ICU-acquired pneumonia, and the unit costs of that resource use. As stated above, the ideal sources for these two categories of economic data are RCTs of SDD. In the event that these

trials do not provide enough information, the use of alternative sources is reported. A summary of the economic data obtained for use in the secondary economic evaluation is provided at the end of this section.

4.4.3.1 Resource Use and Unit Costs Associated with SDD Implementation

The resource use and unit costs associated with the SDD regimen has three components. These are the drug treatment, the microbiological surveillance and the maintenance of side effects of SDD. The SDD trials were examined for economic data in these three areas.

4.4.3.1.1 Resource Use and Unit Cost Associated with SDD Pharmaceutical Regimen

Resource use associated with the SDD regimen was reported by all studies. Review of the trials revealed that 23 studies used the original PTA regimen reported by Stoutenbeek *et al* [1984]. Minor variations include using oral gel instead of paste and gentamicin instead of tobramycin. Variations are detailed in Appendix 4.6 and 4.7. Nineteen trials used SDD for the whole of the patient's stay on ICU. Thirteen trials used it only whilst the patient was ventilated. Fourteen trials reported using intravenous therapy. Ten used cefotaxime, as recommended by Stoutenbeek *et al* [1984]. Appendix 4.8 outlines the range of cefotaxime doses reported. Other trials have used ceftriaxone, ceftazidime, trimethoprim or ofloxacin.

The common resource use reported was PTA liquid and paste (or gel) used four times a day for the whole ICU stay, and cefotaxime 1g four times a

day for four days, intravenously.

However, 28 trials out of the 36 originally examined do not report any unit costs of SDD regimens. The costs reported by eight trials are reported in Chapter Three. The quality of cost data is varied. Winter *et al* [1992], Korinek *et al* [1993] and Suter *et al* [1993] did not report the source of the costs or the year from which the costs were derived. Gastinne *et al* [1992] obtained drug costs from their pharmacy department, but did not state what specific costs constituted the final figures used.

Most authors reported acquisition costs of drugs only, not including labour costs of preparing or administering the drugs. Also, the costs were all reported by foreign studies. Therefore the costs of SDD were obtained from British sources. Two British centres using SDD provided preparation and overhead costs (pharmacy departments, personal communications). The Bristol Royal Infirmary reports overall cost of PTA gel per tube as £9.30 (1994). This lasts 4 days so the cost per day is £2.33.

Southampton General Hospital reports overall cost of PGA paste per tube as £4.53 (1994) so the cost per day is £1.13. The components of the nasogastric preparation and the intravenous cefotaxime are available commercially. The costs per day of treatment are derived from drug acquisition costs and pharmacy overhead costs, reported in Table 4.6. An estimated daily cost of SDD therapy is £19.95 per day when the paste is used and £21.15 when the gel is used. As the most common cefotaxime regimen is 1g qds for four days, the total cost of the course is £92.56.

Table 4.6 Estimated Unit Costs of SDD Regimen Components[1]

DRUG	Quantity & strength of preparation	Cost per unit/£	Dose per day	Cost per day/£[2]
AMPHOTERICIN	12ml (100mg/5ml)	2.31	500mg qds	4.43
COLISTIN	80ml (0.25mu/5ml)	3.98	2mu qds	2.29
TOBRAMYCIN	80mg/2ml vial for injection	2.63	80mg qds	12.10
GENTAMICIN	80mg/2ml vial for injection	1.59	80mg qds	7.31
CEFOTAXIME	1g vial for injection & 10ml WFI	4.95 0.08	1g qds	23.14
CEFOTAXIME	2g vial for injection & 20ml WFI	9.90 0.17	2g tds	34.74

[Prices from British National Formulary, September 1994]

[1] See abbreviations list

[2] Pharmacy overhead: 15% of acquisition cost added (Buxton *et al* [1985]).

4.4.3.1.2 Resource Use and Unit Cost of Microbiological Surveillance of SDD

The reasons for intense microbiological surveillance when SDD is used are discussed in Chapter Three. The most common microbiological surveillance policy reported in the SDD trials is oropharyngeal, rectal, urine, tracheal aspirate and gastric aspirate samples on admission to ICU; and then oropharyngeal, rectal, tracheal aspirate and gastric aspirate samples twice a week (see Appendix 4.10).

However, this intensive type of surveillance results from clinical trial protocols. It would not be expected for this intensity of microbiological surveillance to be common clinical practice. The surveillance in the trials is intended to determine which patients become disinfected, the types of infections and to monitor the emergence of resistant bacterial strains. In clinical practice microbiological cultures are usually only employed when presence of infection is suspected. The implementation of SDD in a practice setting would demand more environmental monitoring to assess emergence of resistant bacteria. Therefore there should be some regular surveillance, but not as much as is demanded by clinical trial protocols. This provides the possibility for a range of microbiological surveillance scenarios. This can be simplified into three resource use models, a method used by Buxton *et al*, [1992]:

1. Resource sparing (minimum regimen possible): Only culture tracheal aspirate swabs when respiratory infection is suspected.
2. Resource moderate (minimum regimen required to adequately monitor SDD): Oropharyngeal and rectal swabs on admission, then twice a week.
3. Resource intensive (most common regimen reported in trials): Oropharyngeal, rectal, gastric aspirate and urine cultures on admission, then oropharyngeal, rectal and gastric aspirate cultures twice a week.

Although some SDD studies report charges of microbiological tests, none are British. Again, it was considered appropriate to use current British unit costs. British costs obtained and detailed in Appendix 4.11 are used in the analysis. The costs of these three models are reported in Table 4.7.

Table 4.7 Estimated Costs of Microbiological Surveillance

Model	Cost on admission/£	Cost during stay/£
Resource sparing	0	8.82 on suspicion of pneumonia
Resource moderate	17.09	17.09 every 3rd day
Resource intensive	30.32	25.91 every 3rd day

4.4.3.1.3 Cost Associated With the Maintenance of Side Effects Arising From SDD

No side effects have been reported in the SDD trials. Emergence of resistant bacterial strains has not been reported. Therefore, in the absence of evidence to the contrary, it is assumed that there are no costs associated with the maintenance of side effects arising from SDD.

The SDD regimen selected for use in the economic evaluation is summarised in the table below. This is referred to as the 'resource moderate' regimen. To assess the effect of more or less intensive SDD regimes on cost/outcome ratios, a 'resource sparing' and a 'resource intensive' model are also summarised in the table. The resource sparing regimen uses daily PTA, the lowest level of microbiological surveillance and no cefotaxime. The resource intensive regimen uses the highest level of microbiological surveillance, cefotaxime and daily PTA. The impact of these models is examined in the sensitivity analysis.

Table 4.8 Summary of SDD Regimens Proposed for Use in Economic Evaluation

Component of Regimen	Resource Sparing Regimen	Resource Moderate Regimen	Resource Intensive Regimen
Cost of PTA gel and liquid per day/£	21.15	21.15	21.15
Cost of Cefotaxime 1g iv qds for 4 days/£	-	92.56	92.56
Cost of microbiological surveillance on admission/£	0	17.09	30.32
Cost of microbiological surveillance twice a week/£	8.82[1]	17.09	25.91

[1] On suspicion of pneumonia only

4.4.3.2 Resource Use and Unit Costs Associated With ICU-Acquired Pneumonia

Resource use resulting from ICU-acquired pneumonia can be divided into two parts. The first is the resultant increase in stay on the ICU and increase of overall hospital stay. The second is the increase in treatment resulting from infection. The unit costs associated with this resource use that are required are costs per day on an ICU and the unit costs of resources associated with treating ICU-acquired pneumonia.

4.4.3.2.1 Evidence for Increased Length of ICU Stay due to ICU-Acquired Pneumonia

The review in Chapter Three has suggested that ICU-acquired pneumonia increases length of ICU stay. 14 SDD trials report lengths of ICU stay for SDD-treated and non-SDD-treated patients. Only one reports a reduction in length of ICU stay between SDD-treated and non-SDD treated groups (Suter *et al* [1993]: 18.5 to 12.7 days, p=0.023). Other trials report no significant reduction in length of ICU stay. Data from the trials that reported length of ICU stay in each of the three original subgroups of trials were used to derive pooled estimates for length of ICU stay in SDD and non-SDD treated patients. Table 4.9 reports this analysis. The weighted means are 18.03 days (sd=9.85) for non-SDD treated and 17.51 days (sd=10.62), calculated from 1309 patients. This length of stay is higher than the average ICU stay for all ICU patients, because these patients are the more severely ill portion of the ICU population. It can be seen that there is a small and non-statistically significant effect size.

Table 4.9 Effect of SDD on Length of ICU Stay of Trials Groups

Length of ICU stay (days)	All trials weighted means[1]	Mixed ICU model weighted means[1]	Surgery/trauma model weighted means[1]
Base length of ICU stay	18.03 (1266, 8.13-27.93)	18.57 (1004, 6.67-30.47)	18.75 (793, 4.25-33.25)
SDD-treated length of ICU stay	17.51 (1266, 6.91-28.11)	18.00 (1004, 5.40-30.60)	18.81 (793, 3.01-34.61)
Effect size[2]	0.52 (2532, -0.68-1.72)	0.57 (2008, -0.83-1.97)	0.06 (1586, -1.54-1.66)

[1] Numbers in parentheses are total numbers of patients included in derivation of weighted mean, 95% confidence interval.

[2] Negative values in 95% CI indicate that there are studies reporting an increase in length of stay in SDD-treated groups.

This lack of a significant difference between SDD and non-SDD treated groups may be due to the grouping together of infected and uninfected patients in the control and treatment groups. The impact of grouping the patients together in this way is illustrated by examination of results reported by Verhaegen *et al* [1992]. They are the only SDD researchers to separate length of stay of infected patients from that of uninfected patients. The table below demonstrates that the change in length of stay from SDD-treated to placebo-treated patients is insignificant. However, when the two groups are divided according to presence or absence of pneumonia, there is a significant increase in length of ICU stay in both SDD and placebo-treated patients who acquire pneumonia.

Table 4.10 Impact of Pneumonia and SDD on ICU Length of Stay [Verhaegen *et al*, 1992]

Length of stay	Placebo group Mean (SD)/days	SDD treated group Mean (SD)/days
Patients without pneumonia	10.6[1] (5.8)	12.4[2] (8.8)
Patients with pneumonia	27.9[1] (18.6)	33.6[2] (20.1)
Increase due to pneumonia	17.3	21.2
All patients	18.9[3] (16.0)	22.4[3] (18.5)

[1] Comparison between infected and uninfected group: $p<0.0001$

[2] Comparison between infected and uninfected group: $p<0.0001$

[3] Comparison between placebo and SDD-treated group: no significance shown.

This study reports an increase in the order of 20 days between infected and uninfected patients. The increase is so large because it is not adjusted for other factors affecting length of ICU stay, as discussed in Chapter Three, section 3.3.1. There are a variety of methods for estimating increased length of ICU stay associated with ICU-acquired pneumonia, as discussed in Chapter Three. Epidemiological studies and SDD trials have failed to demonstrate significant changes in length of stay due to pneumonia or SDD due to inappropriate groups for comparison and insufficient patients. In order to obtain a base value for increase in length of stay from pneumonia, a value has been synthesized from the SDD trial literature in the same way as mortality (Appendix 4.4). The derived ICU length of stay is 20.2 days in patients who contract ICU-acquired pneumonia. ICU length of stay is 17.1 days in those who do not. The

derived pneumonia-attributable length of stay is 3.1 days. Due to the derived nature of this value, it is necessary to carry out sensitivity analysis. The ranges for sensitivity analysis need to reflect real ranges of increase in length of ICU stay due to ICU-acquired pneumonia. Chapter Three reports published increases of zero to nineteen days. Four of the five published estimates are ten days or below, so ten days is selected as the upper limit.

If there is considered to be an increase in length of ICU stay due to ICU-acquired pneumonia, there will be an associated increase in the cost of the patient. It is therefore necessary to know the cost of keeping a patient on ICU for a day. The only British cost per ICU day reported in an SDD study was by Jacobs *et al* [1992]. They report a day on ICU costing £1181 in the UK. However, there is no breakdown of this cost, indication of patient population from which it was derived, or the year of the costs. Therefore, it was necessary to use alternative sources for costs. Estimates of 'top-down' or 'bottom-up' costs of one day's stay on ICU are often difficult to obtain because intensive care costs are included in surgery or anaesthetics department costs. Ridley *et al* [1991] carried out an individual patient 'bottom-up' costing study on intensive care, as discussed in Chapter Two. The mean cost of a British ventilated patient in 1989 was reported as £726 (95% CI: £656-795). Inflating to 1994/95 prices using the Health Services Prices Index gives a mean value of £886 (95% CI: £849-970).

Sensitivity analysis of the effect of smaller costs per day (as would be expected at a district general hospital) and larger costs per day (as would be expected at a teaching hospital) is undertaken. In the absence of more reliable evidence, a cost per ICU day at a DGH was suggested to be about £800. A day on a teaching hospital ICU was suggested to be £1000 [personal communication, finance department, Charing Cross Hospital, 1994]. These two values were used as high and low estimates of cost per

day. However, there is a wide variation in cost per ICU day within a single ICU, as illustrated in Chapter Two. The impact of this was examined by setting the sensitivity ranges at £500 and £1500.

4.4.3.2.2 Evidence for Increased Therapeutic Activity Associated with ICU-Acquired Pneumonia

An episode of ICU-acquired pneumonia may be expected to lead to increased resource use and thus incur increased costs. Resource use arising from extra therapeutic intervention may include antibiotics, X-rays, physiotherapy, microbiological surveillance and prolonged ventilation. Very little information on treatment of ICU-acquired pneumonia was found in SDD trials. The two areas investigated most were the number of therapeutic antibiotic days and microbiological surveillance.

Therapeutic Antibiotics and Other Drugs

11 SDD trials report antibiotics used to treat infections. A significant drop was reported from control to SDD-treated groups, expressed as number of antibiotic days. Details of which agents were used were not given. Total costs only are reported, rather than levels of resource use and associated unit costs. Korinek (France, 1993) reported a mean cost per patient of US$556(sd=506) in control patients and US$469 (sd=413) in SDD treated patients (US$, 1989). Gastinne (France, 1992) reported a mean cost per patient of US$158 (sd=691) in control patients and US$53 (sd=202) in SDD treated patients (US$, 1992). Rocha (Spain, 1989) reported a mean cost per *infected* patient of 119660 Pta (Pta, 1989, Oct 1994: £1=203.99Pta, inflating to 1994, 119660 Pta = £748.66). No

significance tests were reported. The two French authors do not differentiate between infected and uninfected patients. The Spanish study does. However, none of these trials is British, so the data have limited applicability to a British setting. Also, the costs reported are just the acquisition cost. Antibiotics have a variable amount of associated costs from disposables, serum level monitoring requirements and management of side effects. In the absence of any other data, the antibiotic costs reported by Rocha *et al* [1989] are used.

Other drugs, disposables and disinfectants used as a consequence of ICU infections have been reported in a Belgian study by de Clerq [1983]. The sources are not quoted and no significance tests are reported. The infection-attributed increase in costs of laboratory material, sterile disposables and disinfectants is 891.1 BFr at 1983 prices. Inflating to 1994 (Oct 1994: £1 = 50.2BFr), this equates to £17.75. Infection-attributed costs of other drugs and infusion fluids are quoted as 969BFr per day, which is equivalent to £33.01 per day [1994]. These costs were the only published information available.

Pneumonia-Attributable Investigations

Increased pathology and radiology testing may be expected as a result of pneumonia. However, little relevant work has been carried out in the UK. No SDD trials report relevant information. Coello *et al* [1993] carried out a matched cohort study of hospital acquired infection in surgical patients in a DGH. They report significantly higher utilization of microbiology ($p<0.0001$), haematology ($p<0.001$), chemical pathology ($p<0.001$) and radiology ($p<0.007$) in infected hospital patients. No evidence to this effect was found in ICU-acquired pneumonia. In the absence of any other

information, the increases in numbers of tests and costs of tests reported by Coello *et al* [1993] can be used as conservative estimates. The increased cost in microbiology is £18.80 (1994: £19.74), radiology is £8.00 (1994: £8.40), haematology is £18.10 (1994: £19.01) and chemistry is £12.10 (1994: £12.71).

The combination of cost data on antibiotics used to treat pneumonia (£748.7 [Rocha *et al*, 1993]), pneumonia-attributable investigations (£59.9 [Coello *et al*, 1993], other drugs attributable to pneumonia (£666.8 [de Clerq *et al*, 1983]) and pneumonia-attributable equipment (£17.8 [de Clerq *et al*, 1983]) gives a cost of £1493 to treat an episode of ICU-acquired pneumonia. It is known that this estimate is not very accurate. However, the degree of uncertainty is unknown, making selection of sensitivity analysis ranges more difficult. Arbitrary ranges of 50% (£750) to 150% (£2250) have been selected to enable investigation of the impact of variation of this area of cost on the cost/outcome ratios.

4.4.3.3 Summary of Costs of Patients for Base Case Scenario

Table 4.11 summarises the resource use and cost evidence reported in this section. The two main categories of cost are those from SDD implementation and from ICU-acquired pneumonia treatment. The point estimates for the cost categories are reported, as well as their ranges for sensitivity analysis.

The decision-analytic model requires costs for infected and uninfected patients, in the event of either having or not having SDD. These four costs are derived from the economic evidence listed. The cost of a ventilated patient who does not contract an ICU-acquired pneumonia is derived from

the published cost per ICU day and the derived length of ICU stay for an uninfected patient, to give the value of £15151. This cost is then adjusted in the event of an episode of pneumonia by adding the cost of extra days on ICU and the treatment cost associated with pneumonia, to give a value of £19390. If SDD is used, the costs associated with SDD are added to these costs to give £15717 for an uninfected patient and £20036 for an infected patient.

Table 4.11 Summary of Costs of Patients for Economic Evaluation of SDD

Cost component	Cost per infected patient/£	Cost per uninfected patient/£
Length of ICU stay (days)[1]	20.2	17.1
Cost per day on ICU [Ridley, 1991][2]	886.0	886.0
Antibiotics to treat pneumonia [Rocha, 1989][3]	748.7	0
Pneumonia attributable investigations [Coello, 1993]	59.9	0
Other drugs attributable to pneumonia [de Clerq, 1983]	666.8	0
Pneumonia-attributable equipment [de Clerq, 1983]	17.8	0
Total cost per non-SDD ICU patient	19390	15151
Cost of drugs associated with SDD regime[4]	519.8	454.2
Cost of microbiological investigation associated with SDD	126.2	111.8
Total cost per ICU patient on SDD	20036	15717

[1] Increase in length of ICU stay: 3.1 days: varied from 0 to 10 days.

[2] Cost per day varied from £500 to £1500.

[3] Total cost of pneumonia treatment: £1493; varied from £750 to £2250.

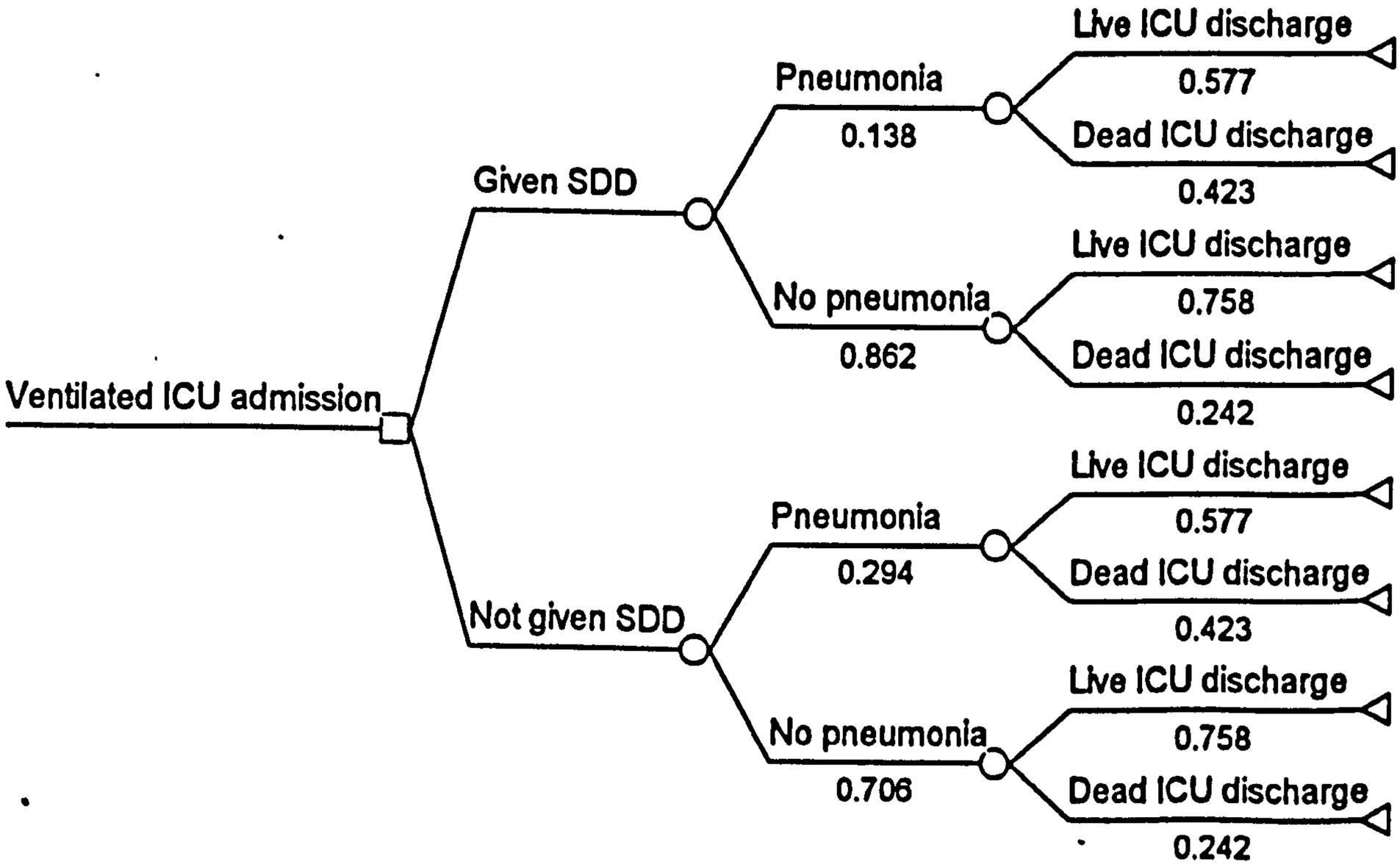
[4] SDD regimen more and less resource intensive in sensitivity analysis

4.4.4 Derivation of Cost/Outcome Ratios for SDD

The third stage of the economic evaluation is to derive cost/outcome ratios for SDD compared with its alternatives. This is done by attaching clinical probabilities and economic cost data to the decision analytic model to derive incremental cost/outcome ratios. A 'base case' model is produced first using point estimates derived from extracted clinical and economic data.

Firstly, clinical probabilities were attached to the decision-analytic model, from Table 4.5, as shown in Figure 4.3. This was to allow overall path probabilities to be calculated. Clinical probabilities were attached to each part of Tree A.

Figure 4.3 Decision-Analytic Model of SDD, Including Clinical Probabilities



However, clinical probabilities could not be attached to Tree B which considers the long term effects of SDD and pneumonia on life expectancy. because there was no available evidence on the effect of pneumonia or SDD on life expectancy and quality of life. This tree was collapsed into a single outcome that assumes that ICU survivors acquire 17.3 LYGs and 6.3 dQALYs whether they acquire pneumonia or are given SDD or not. The economic data was also attached to the decision-analytic model, as summarised in Table 4.11. The cost associated with each pathway is then added to each pathway. No costs were available beyond ICU discharge. This restricts the perspective of the analysis to that of the ICU.

The treatment and control arms of Tree A can be interpreted in the following way. A ventilated patient is admitted to ICU with a probability of 0.294 of contracting ICU-acquired pneumonia. If he contracts pneumonia he costs the ICU £19390 and has a 42.3% risk of death on the ICU. If he does not contract pneumonia, he costs the ICU £15151 and has a 24.2% risk of death on the ICU. In either situation, if he survives ICU, he gains 17.3 life years and 6.3 dQALYs. The branch of the model where SDD is administered is interpreted in the same way. It is necessary to combine the costs and outcomes of the pathways within the model in such a way as to elucidate the incremental cost and outcome differences between SDD and the control. This was done by applying a theoretical cohort of 2000 ventilated ICU patients to the model. One thousand were modelled to receive SDD and one thousand entered the control arm. Without the use of SDD, 294 patients contracted pneumonia and 295 died on ICU, at a total cost of £1.640×10^7. The 705 survivors gained 12196.5 life years and 4441.5 dQALYs in total. Of the 1000 patients treated with SDD from ICU admission, 138 contracted pneumonia and 267 died on ICU at a cost of £1.631×10^7. The 733 survivors gained 12680.9 life years and 4617.9 dQALYs in total. The overall incremental *decrease* in cost associated with

the patients who receive SDD is £0.09x10^7. This decrease in cost is associated with 156 fewer episodes of pneumonia, 28 fewer ICU deaths, an additional 484 life years gained and 176 added dQALYs. As the clinical outcomes are improved by SDD at a lower cost, SDD is the *dominant* therapy. This analysis is reported in Table 4.12.

The results of this economic evaluation suggest that SDD is a dominant therapy, which, in turn, suggests that SDD should be implemented in ICUs to improve patient outcomes at a decreased cost to the unit. However, the process of acquisition of clinical and economic evidence reported in sections 4.4.2 and 4.4.3 has uncovered many areas where there is a lack of good, or any, data. The reduction in pneumonia rates has narrow confidence intervals. However, some clinical parameters, such as quality of life and life expectancy are based on poor quality data. Most economic parameters are based on deterministic point estimates of poor quality. These data either have wide ranges of variation, such as increase in length of ICU stay by pneumonia, or the degree of uncertainty is not known at all, such as cost of pneumonia treatment. The use of data with a high level of attached uncertainty necessarily introduces uncertainty into cost/outcome ratios. It is possible that variation in these parameters may significantly affect cost/outcome ratios.

Table 4.12 Incremental Economic Analysis of SDD in ICU-Acquired Pneumonia Prevention

Strategy	Data			Incremental Comparison	Outcome measures			
	Cost/1000 (£)	Infections /1000	Deaths /1000	Cost/£	Infections prevented	Lives saved	Life years gained	dQALYs gained
No SDD	1.640×10^7	294	295	0	0	0	0	0
SDD	1.631×10^7	138	267	(0.09×10^7)	156	28	484	176

No SDD: For 1000 patients, 294 contract infection at cost of £19390 per patient

706 do not, at a cost of £15151 per patient.

Total cost = (294x19390) + (706x15151) = **$£1.640 \times 10^7$**

SDD: For 1000 patients, 138 contract infections at a cost of £20036 per patient

862 do not, at a cost of £15717 per patient.

Total cost = (138x20036) + (862x15717) = **$£1.631 \times 10^7$**

4.4.5 Sensitivity Analysis of the Economic Analysis of SDD

The conclusion that SDD is a dominant therapy relates only to the conditions defined in the base case detailed in section 4.4.4. Cost effectiveness and cost utility measures calculated for SDD have necessarily proceeded by making assumptions about the clinical and economic evidence. It is necessary to test the sensitivity of this dominance to these assumptions. This section tests the sensitivity of the conclusions derived to the data used. This is done by varying the clinical and economic parameters to see how sensitive the conclusions are to these variations. The extent to which the conclusions can be changed by varying parameters gives an indication of the robustness of these conclusions. The ranges of the variation of the parameters are used as outlined in the previous section. The parameters examined are variation in SDD effectiveness in reducing pneumonia rates; base pneumonia rates; pneumonia-attributable mortality; cost of different SDD regimens; increased length of ICU stay due to pneumonia; cost per ICU day and costs associated with pneumonia treatment.

4.4.5.1 Effect of Changing Decrease in Pneumonia Rate by SDD

The reduction in pneumonia rate by SDD ultimately effects all other outcomes, mortality, LYGs and QALYs, so it is an influential variable. The reduction in ICU-acquired pneumonia rate by SDD is 53% (95% CI: 43 to 63%). The narrow confidence interval indicates the high level of precision of the estimate. The sensitivity analysis examines the variation of cost/outcome ratios within these ranges. However, reported efficacies of SDD range from 10 to 80%, so the effect of this amount of variation is also examined. Table 4.13 summarises the effect that these variations in reduction in pneumonia rate have on cost per pneumonia avoided, cost per death averted, cost per LYG and cost per dQALY

gained.

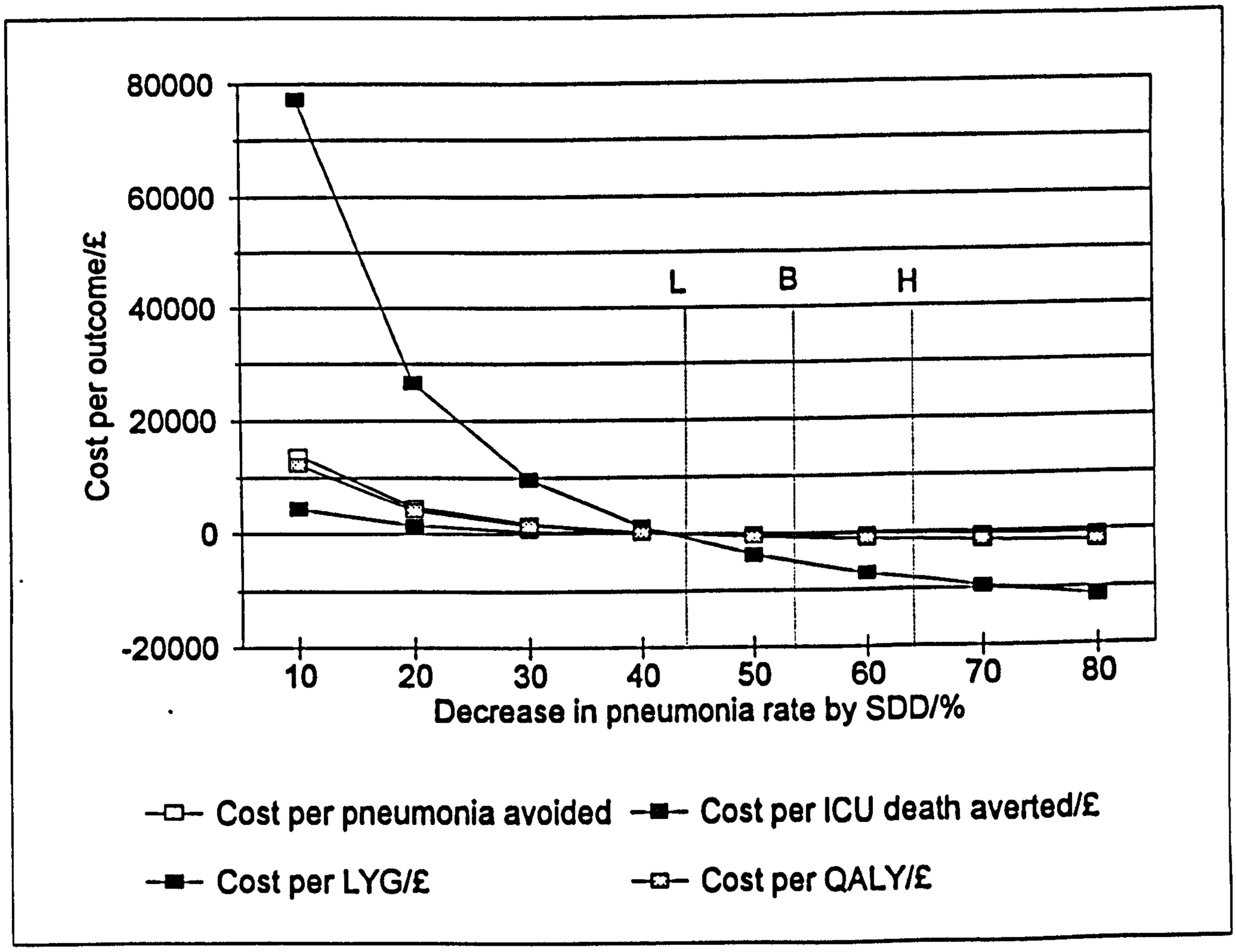
Figure 4.4 illustrates the impact of changing the decrease in pneumonia rate, in stages from 10% to 80%. The base case (B) where there is 53% reduction and the low (L) and high (H) limits of the 95% confidence intervals are marked on the graph. Cost/outcome ratios become smaller as the effectiveness increases. Cost per death averted shows the largest variation. SDD becomes dominant for all ratios above 42% reduction in pneumonia rate. The pneumonia reduction rate has a large effect on cost/outcome ratios between the extreme ranges. However, the cost/outcome ratios do not vary dramatically within the 95% confidence intervals.

Negative cost/outcome ratios imply that SDD is the dominant therapy. It is important to note that, in this sensitivity analysis and all subsequent reported by this thesis, that the values of these cost/outcome ratios are meaningless in terms of decision-making. They illustrate only that the therapy remains dominant for a wide range of SDD effectiveness values. The conclusion that SDD is dominant does not change, that is, it is robust, unless the effectiveness of SDD is assumed to drop below 42%. In this situation, improved outcomes (reduced infections and so on) are achieved at a higher cost. When this is the case, it is appropriate to quote cost/outcome ratios.

Table 4.13 Effect of Variation of Reduction in Pneumonia Rate by SDD on Cost/Outcome Measures

Reduction in pneumonia rate by SDD/%	Cost per pneumonia avoided/£	Cost per ICU death averted/£	Cost per LYG/£	Cost per dQALY gained/£
10% (lower limit)	15913	88586	5130	14109
43% (lower 95% CI)	338	1761	109	381
53% (base value)	-577	-3214	-186	-511
63% (upper 95% CI)	-1147	-5976	-370	-1017
80% (upper limit)	-1822	-9475	-587	-1615

Figure 4.4 Graph to Show Variation of Cost/Outcome Ratios with Variation in Pneumonia Rate Reduction by SDD



L: Low estimate for decrease in pneumonia rate (43%)

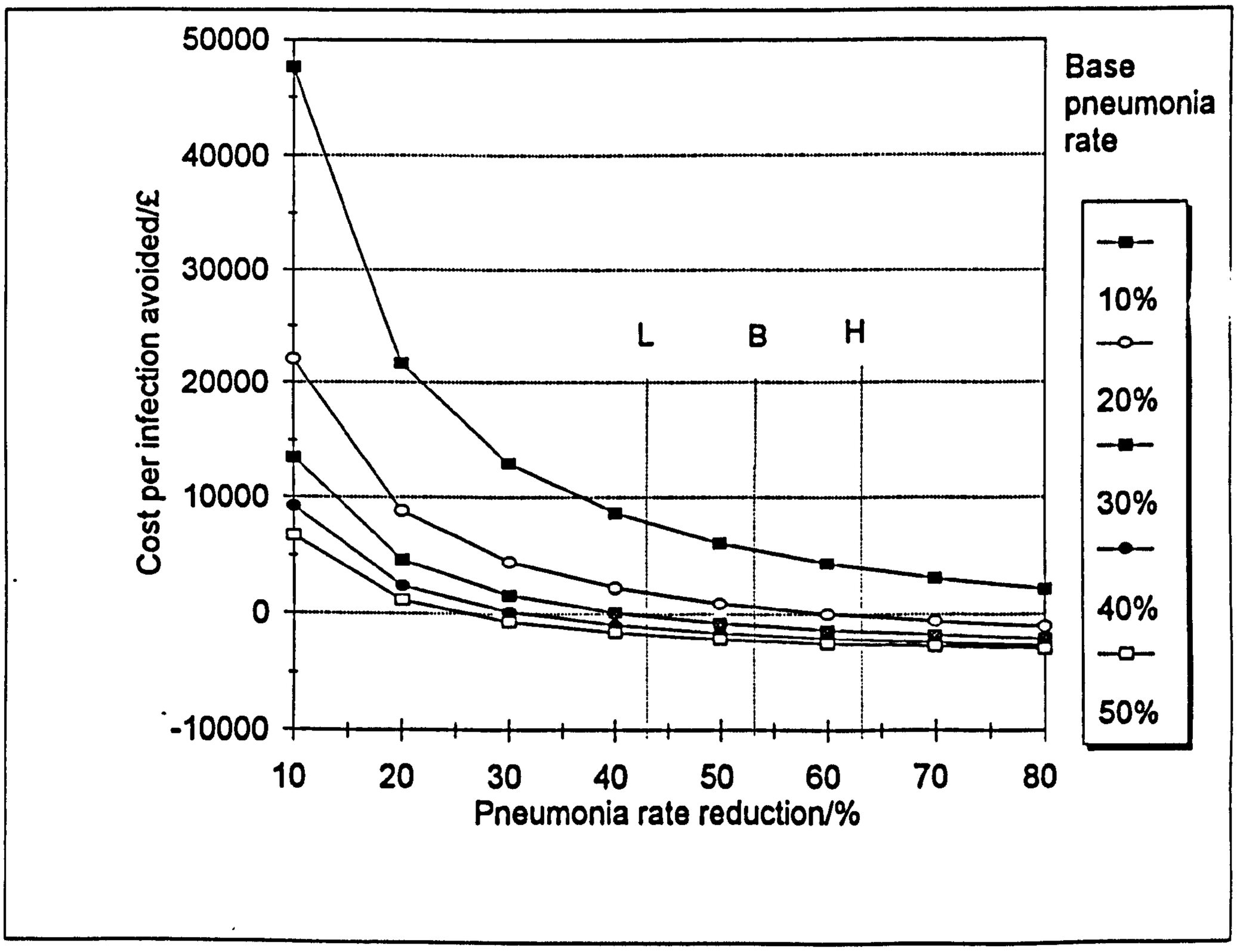
B: Base estimate for decrease in pneumonia rate (53%)

H: High estimate for decrease in pneumonia rate (63%)

4.4.5.2 Effect of Changing Base Pneumonia Rate

The ICU-acquired pneumonia rate of the control arm was varied to see to what extent variation in local incidence rates would affect cost/outcome ratios. The base pneumonia rate was varied from 10% to 50%. This reflects the range of pneumonia rates reported in ICUs, as discussed in Chapter Three. Figure 4.5 illustrates the variation of pneumonia rate reduction by SDD with base pneumonia rates. It can be seen that the higher the base pneumonia rate is, the more cost effective SDD is shown to become at each level of effectiveness of SDD. The lower the base pneumonia rate, the larger the reduction in that rate required to achieve low cost/outcome ratios. SDD becomes the dominant therapy at lower levels of effectiveness the higher the base pneumonia rate. This pattern was the same when this analysis was applied to the other cost/outcome ratios. Therefore, the base pneumonia rate of any particular ICU will affect the opportunity that SDD has to be cost effective. The conclusion that SDD is a dominant therapy is very dependent upon this parameter. Therefore, uncertainty around it greatly decreases the robustness of the conclusions.

Figure 4.5 Graph to Show Variation of Cost per Pneumonia Avoided with Reduction in Pneumonia Rate for a Range of Base Pneumonia Rates



L: Low estimate for decrease in pneumonia rate (43%)

B: Base estimate for decrease in pneumonia rate (53%)

H: High estimate for decrease in pneumonia rate (63%)

4.4.5.3 Effect of Changing Mortality Effects of Pneumonia

The use of derived mortalities for infected and uninfected mortality, rather than values taken directly from research decrease the confidence with which the values can be used. The base case model uses a reduction of 9.5% mortality in the SDD group. This sensitivity analysis examines the impact of an increase or decrease in this mortality reduction. The number of deaths averted by SDD (and thus life years and dQALYs gained) is dependent upon the reduction in pneumonia rate. The change in resource use due to the implementation of SDD is not affected. SDD is dominant, so any deaths averted occur in conjunction with a reduction in cost. It is not appropriate, therefore, to quote cost/outcome ratios. Instead, the effect on numbers of deaths averted, number of LYGs and dQALYs gained if the mortality of the group is assumed to be reduced by 0 to 20% if SDD is used is examined. If mortality is not reduced by SDD there will be no deaths averted and no associated LYGs or QALYs gained. If the mortality is reduced by 20%, there will be 59 deaths averted, 1020.7 LYGs and 371.7 dQALYs gained. At either extreme, the resource use saving will still be £90000. Therefore, the conclusion that SDD is dominant is not affected by variations in the reduction of mortality. So, the conclusions are robust with respect to this parameter.

The second area of uncertainty here is the precision of the estimates for LYGs and dQALYs. The values for LYGs and dQALYs are very tentative due to their sources. The significant uncertainty surrounding these values is reflected in their wide, and largely arbitrary, ranges for sensitivity analysis. The sensitivity ranges selected for LYGs and dQALYs gained from Table 4.5 are used to derive ranges for these outcome measures. The results of this analysis are reported in Table 4.14. The values for LYGs and dQALYs gained by ICU survivors in this model are very tentative and rely entirely upon the decrease in mortality.

However, the conclusion that SDD is dominant is not affected by variations in the numbers of life years or QALYs gained. So, the conclusions are robust with respect to these parameters, even though there is much uncertainty associated with them.

Table 4.14 Effect of Variation of LYGs and dQALYs Gained by ICU Survivors

Outcome parameter	Units of outcome gained per 1000 patients	Sensitivity Analysis Range
ICU deaths averted	28	-
Life years gained	484	244-728
dQALYs gained	176	22-277

4.4.5.4 Effect of SDD Regimen

Variation in the resource use associated with the SDD regimen itself may have an impact on cost/outcome ratios. Table 4.15 summarises the effect of using the three regimens outlined in the previous section. It can be seen that SDD remains the dominant therapy for all three alternatives. Therefore, the conclusion that SDD is dominant is robust with respect to this parameter.

Table 4.15 Effect of Intensity of SDD Regimen on Cost/Outcome Ratios

SDD Regimen	Cost per pneumonia avoided/£	Cost per ICU death averted/£	Cost per LYG/£	Cost per dQALY gained/£
Resource sparing	-2145	-11952	-691	-1902
Resource moderate	-577	-3214	-186	-511
Resource intensive	-218	-1217	-70	-194

4.4.5.5 Effect of Increase In Length of ICU Stay by Pneumonia

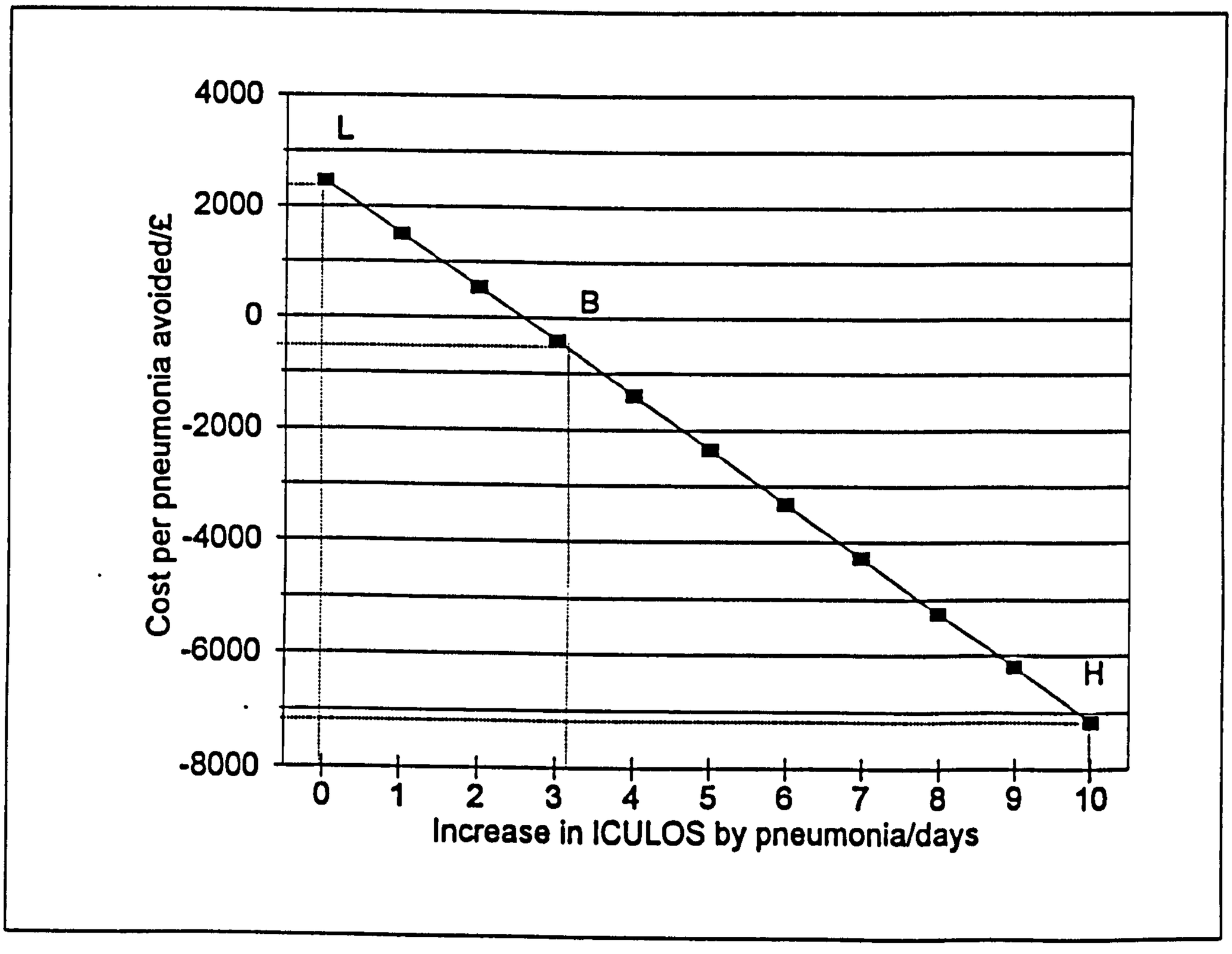
The difference in length of stay between infected and uninfected patients was derived as 3.1 days in section 4.4.3. An increase of 0 to 10 days is employed as the range in the sensitivity analysis. Table 4.16 summarises the effect of this variation on the cost/outcome ratios. It can be seen that there is very large effect on the ratios when this parameter is varied. This is illustrated in Figure 4.6 where the variation in cost per pneumonia avoided only is examined. SDD therapy remains the dominant therapy if the increase in length of ICU stay is assumed to be at least 2.7 days.

The conclusion that SDD is a dominant therapy is very dependent upon this parameter. Therefore, uncertainty around it greatly decreases the robustness of the conclusions.

Table 4.16 Effect of Variation of Length of Stay Increase Due to Pneumonia on Cost Outcome Measures

↑ Length ICU stay due to pneumonia/days	Cost per pneumonia avoided/£	Cost per ICU death averted/£	Cost per LYG/£	Cost per dQALY gained/£
0 (lower limit)	2470	13761	796	2187
3.1 (base value)	-577	-3214	-186	-511
10 (upper limit)	-7176	-39979	-2313	-2048

Figure 4.6 Graph to Show Variation of Cost per Pneumonia Avoided where Length of Stay Increase in the Presence of Pneumonia is Varied



L: Low estimate for increase in length of ICU stay (1 day)

B: Base estimate for increase in length of ICU stay (3.1 days)

H: High estimate for increase in length of ICU stay (10 days)

4.4.5.6 Effect of Cost per ICU Day

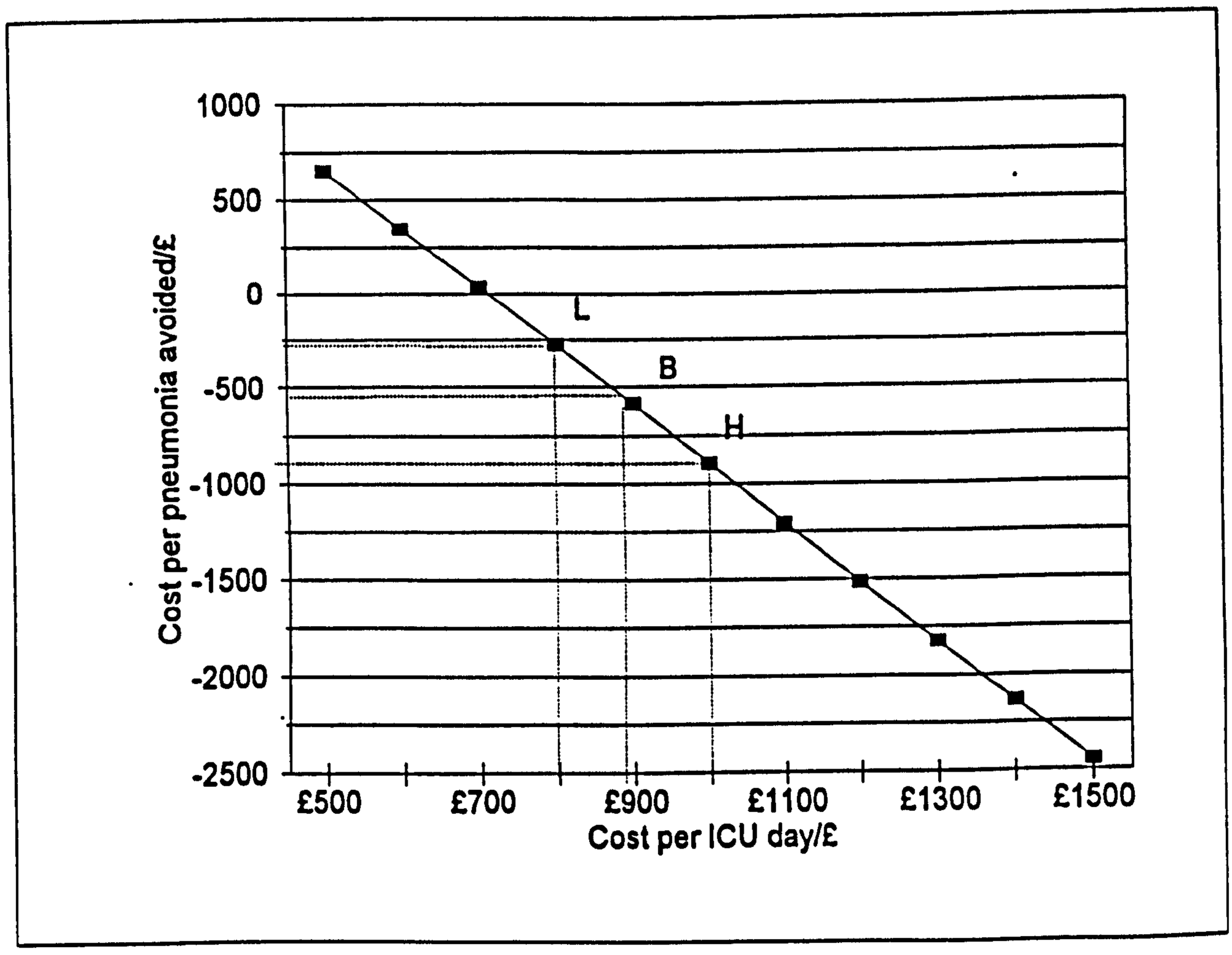
The base case cost/outcome ratios are calculated using a cost per ICU day of £886. A high and low mean daily ICU cost was considered to be £1000 and £800, respectively. Table 4.17 lists the cost/outcome ratios derived from using these three values. To better reflect the range of reported daily costs, extreme ranges of £500 and £1500 were used. This is illustrated in Figure 4.7, using cost per pneumonia avoided only. It can be seen that the higher the daily ICU cost, the more cost effective SDD is shown to be. SDD remains the dominant therapy if the cost per ICU day is greater than £700.

The conclusion that SDD is a dominant therapy is dependent upon cost per ICU day. Therefore, uncertainty around it decreases the robustness of the conclusions.

Table 4.17 Effect of Variation of Cost per ICU Day on Cost/Outcome Ratios

Cost per ICU day/£	Cost per pneumonia avoided/£	Cost per ICU death averted/£	Cost per LYG/£	Cost per dQALY gained/£
800 (lower limit)	274	1577	88	243
886 (base value)	-577	-3214	-186	-511
1000 (upper limit)	-894	-4981	-288	-792

Figure 4.7 Graph to Show Variation of Cost per Pneumonia Avoided where Cost per ICU Day is Varied



L: Low estimate for cost per ICU day (£800)

B: Base estimate for cost per ICU day (£886)

H: High estimate for cost per ICU day (£1000)

4.4.5.7 Effect of Variation in Treatment Intensity of Pneumonia

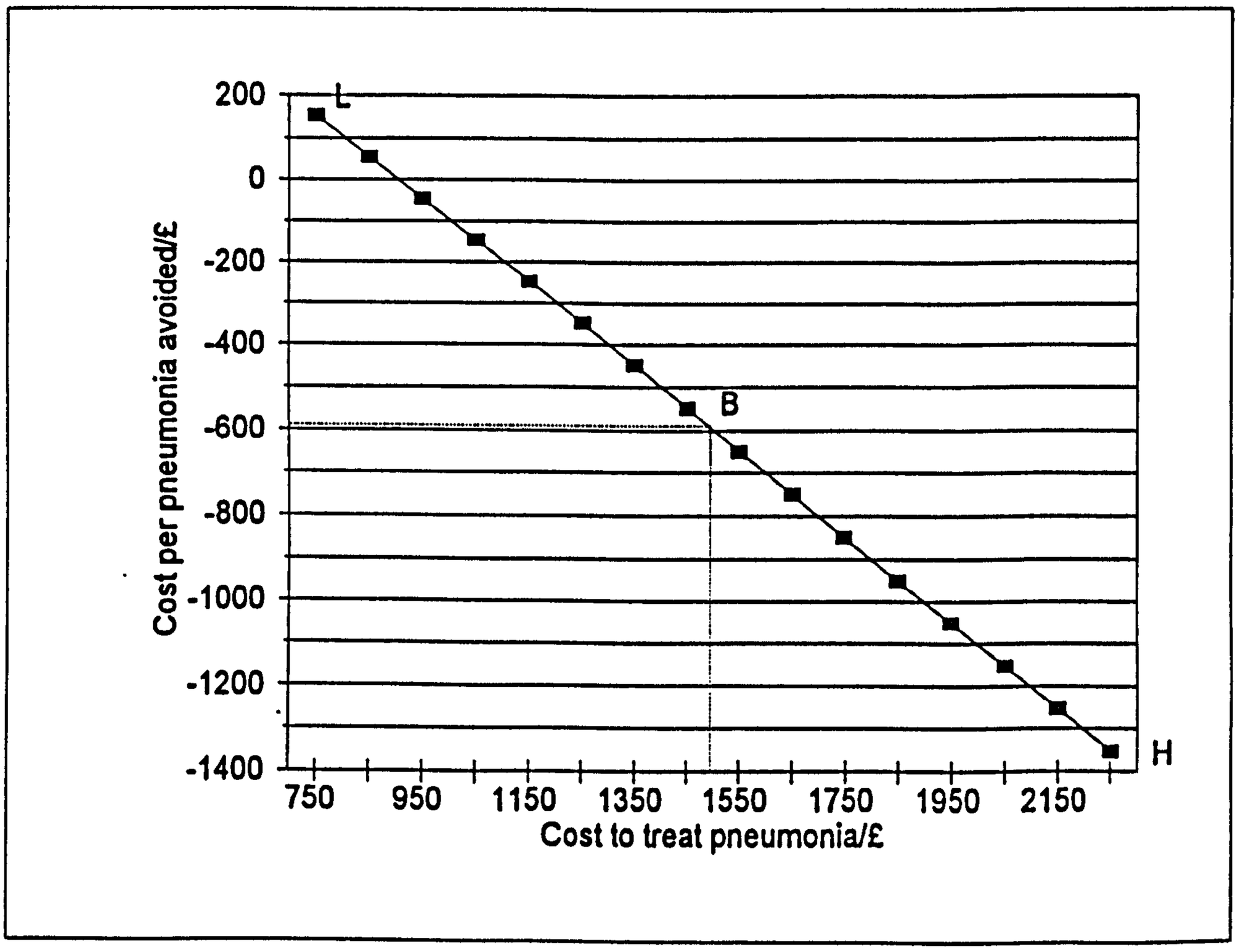
The base case cost/outcome ratios are calculated using a cost of £1493 to treat an episode of ICU-acquired pneumonia. Arbitrary ranges for the cost of treatment were selected as £750 to £2250, respectively. Table 4.18 lists the cost/outcome ratios derived from using these ranges. This is illustrated in Figure 4.8, using cost per pneumonia avoided only. It can be seen that the higher the cost of treating pneumonia, the more cost effective SDD is shown to be. SDD becomes the dominant therapy if the cost of treating pneumonia is greater than £900.

The conclusion that SDD is a dominant therapy is dependent upon the cost of treating an episode of pneumonia. Therefore, uncertainty around it decreases the robustness of the conclusions.

Table 4.18 Effect of Variation of Cost of Pneumonia Treatment on Cost/Outcome Ratios

Cost per ICU day/£	Cost per pneumonia avoided/£	Cost per ICU death averted/£	Cost per LYG/£	Cost per dQALY gained/£
£750 (lower limit)	155	863	50	136
£1493 (base value)	-577	-3214	-186	-511
£2250 (upper limit)	-1353	-7536	436	-1198

Figure 4.8 Graph to Show Variation of Cost per Pneumonia Avoided where Cost of Pneumonia Treatment is Varied



- L: Low estimate for cost of pneumonia treatment (£750)

  B: Base estimate for cost of pneumonia treatment (£1493)

  H: High estimate for cost of pneumonia treatment (£2250)

4.4.5.8 Translating Theoretical Results into Practice

This economic evaluation has suggested that, given the conditions stated, the implementation of SDD in a British ICU reduces the incidence of ICU-acquired pneumonia, at a lower cost. The use of SDD in 1000 theoretical ventilated ICU admissions would result in cost savings of £900,000. This cost saving is due to the prevention of 156 episodes of ICU-acquired pneumonia. 3.1 days extra stay on ICU are therefore avoided per episode. This means that 483.6 patient days are made available, equivalent to 1.32 ICU beds per year. This section examines to what extent these theoretical cost savings can be translated into practice.

In practice, British ICUs have a smaller annual patient admission rate, mostly between 200 and 400 patients per year [Metcalfe *et al*, 1995]. Furthermore, not all these patients would be expected to be eligible for SDD. 57% ICU admissions in the UK are ventilated [Metcalfe *et al*, 1995]. Therefore, the number of eligible patients on an ICU would be more likely to be between 120 and 240. This translates into making available 58 to 116 bed days per year, on a typical ICU. This is alternatively expressed as 0.16 to 0.32 ICU beds made available per year. However, this may not be realised in practice, for a variety of local organisational reasons.

There are two general theoretical scenarios into which SDD is introduced, the first being an ICU operating at higher than optimal occupancy levels, reflected by a high patient admissions refusal rate. The second scenario is SDD being introduced into an ICU operating at a lower than optimal occupancy rate, reflected by a zero patient admissions refusal rate and consistently empty beds. The impact of SDD on occupancy, patient turnover and patient refusal rates is different in the two scenarios, described below.

4.4.5.8.1 High Occupancy Unit

Shorter lengths of ICU stay in a subset of patients means those patients leave the ICU earlier than they would have done without SDD. As this is a high occupancy unit, this means that more patients can be admitted. Therefore, the patient refusal rate may drop, the overall occupancy will remain the same as before and there will be a higher patient turnover. This increase in patient turnover at a constant level of occupancy will affect the resource use of the ICU.

From the point of view of the ICU, SDD could have an overall effect on fixed, semi-fixed and variable costs. If the bed/days made available by SDD are immediately filled, as suggested above, the occupancy of the unit is not decreased. So, the ICU is required to run at the same occupancy level as before. Therefore, there are no implications for reducing fixed costs at the beginning of the next short run. Semi-fixed costs, that is nursing costs, are also not 'saved' in practice, as they will be directed to the extra admissions. Nursing costs may actually be increased by the demands of a higher rate of admission and discharge. Variable costs saved by the shorter length of ICU stay will also not be saved in practice as they will be absorbed by the extra admissions. Therefore, the actual cost savings due to SDD may not be very high at all. Also, there is the added cost of SDD implementation. Therefore, the introduction of SDD could theoretically increase the patient turnover of the ICU, with an increase in variable cost.

However, from the perspective of the refused admissions, the opportunity cost associated with refusal would be avoided. This is discussed in more detail in Chapter Eight.

4.4.5.8.2 Low Occupancy Unit

Shorter lengths of ICU stay in a subset of patients means those patients leave the ICU earlier than they would have done without SDD. As this is a low occupancy unit, this means that it is likely that no more patients will be admitted. This leads to the same patient turnover and a decreased occupancy.

This decrease in occupancy at a constant patient turnover would affect costs. In the short run, fixed costs are not affected by occupancy. Therefore, in reality, these costs are not saved. Medical and nursing costs may also not be saved in reality. In the event of low occupancy, nurses and medical staff are deployed to work on other wards, although a minimum level of staffing has to be maintained on the ICU to be ready for new admissions. The variable costs associated with these unused patient days would be saved. Extra variable costs would be incurred from the implementation of SDD. So in reality, some variable costs could be saved, but the SDD costs, staff and fixed costs would still be incurred.

This shows that local information on unit size, bed occupancy, patient turnover and refusal rates are needed to assess *realisable* cost savings. This issue is handled quantitatively in the economic evaluation in Chapter Eight.

4.5 DISCUSSION OF RESULTS OF SECONDARY ECONOMIC EVALUATION

The main objective of this study was to use the clinical and economic literature to assess the conditions, if any, under which SDD can be demonstrated to be cost effective. The second objective was to assess

whether the methods used were able to generate robust conclusions, or whether further investigation was required.

Section 4.4.1 described the derivation of the research question and the associated decision-analytic model. The model was straightforward with one clinical decision node and four subsequent probabilistic nodes. The process of the SDD intervention was precisely defined. The patient group modelled to receive SDD were ventilated ICU admissions. The alternative to SDD was no treatment. The clinical probabilities and categories of resource use associated with each section of the treatment pathway were identified. Desired outcome measures incorporating long term morbidity and mortality were defined.

The next stage was to attach clinical and economic evidence to the decision-analytic model to enable derivation of incremental cost/outcome ratios. Section 4.4.2 outlined the acquisition of clinical data required by the model. The parameters required were effectiveness of SDD in reducing pneumonia rates, and its effect on short and long term morbidity and mortality. SDD trials were the initial source, 37 clinical trials being retrieved and then reviewed systematically. Using meta-analysis, pneumonia and ICU mortality reduction rates were obtained. This method was very successful for deriving a mean value for reduction in pneumonia rate of 53% with narrow confidence intervals. However, mortality was not reported by the SDD trials in such a way that the data could be used in the decision-analytic model. This necessitated further processing of the data. It could not be unequivocally concluded that SDD reduces ICU mortality, but the results of the meta-analysis suggest that there is a relationship. Published meta-analyses discussed in Chapter Three suggest that there is a relationship, although epidemiological studies of the effect of ICU-acquired pneumonia on mortality were not able to indicate an independent relationship. No evidence was available from the trials regarding the impact of SDD or

ICU-acquired pneumonia on quantity and quality of life. Alternative sources were examined. This did not provide any information about the impact of ICU-acquired pneumonia on short and long term morbidity and mortality. The evidence for LYGs was taken from age-specific life expectancy tables, rather than being derived from an ICU population. The evidence for QALYs (discounted) was taken from a study of ICU patients. It was not possible for either dataset to differentiate between patients who do or do not acquire pneumonia.

Section 4.4.3 described the acquisition of economic evidence, which consisted of resource use and associated unit costs. The categories required were the resource use and costs associated with SDD implementation and those associated with the treatment of ICU-acquired pneumonia. The SDD trials provided very little evidence, apart from some reporting of costs of SDD regimens. However, the source and components of these costs were not known and they were mostly from foreign studies. Alternative sources were investigated for economic information. The SDD regimens reported by the trials were costed for use in this country using British costs of drugs and microbiological tests.

Costs associated with the treatment of ICU-acquired pneumonia were inadequately characterised. These costs divide into the increase in length of ICU stay, the increase in treatment intensity whilst on ICU, and subsequent effects on resource use on the ward. The literature reported varying increase in length of ICU stay due to pneumonia. The increase in length of stay was derived from the fourteen SDD trials that reported length of stay. Costs attributable to pneumonia treatment were derived from a variety of sources. This category of economic data was the least satisfactorily quantified by published evidence. No evidence was found on the resource use of the patient once they have left ICU.

Using the clinical and economic evidence available, an incremental economic analysis of SDD was carried out in section 4.4.4. The outcome measures used were pneumonias avoided, ICU deaths avoided, LYGs and dQALYs gained. Within the assumptions of the base case, SDD was less costly and more effective, that is, dominant.

The clinical and economic evidence was demonstrated to be unsatisfactory in many areas. The lack of robustness in the evidence is reflected by the wide ranges recommended for use in the sensitivity analysis. If the conclusion that SDD is dominant is changed by varying these underlying parameters, then the conclusions are not robust. To assess the sensitivity of the conclusions to variations in different clinical and economic parameters, a sensitivity analysis was carried out in section 4.4.5. This sensitivity analysis showed that SDD remained dominant through most degrees of variation for most parameters. The parameters that reversed the conclusion that SDD was dominant, when varied sufficiently, were effectiveness of SDD, base pneumonia rates, increase in length of ICU stay by pneumonia, cost per ICU day and costs associated with treating pneumonia.

SDD lost dominance if its effectiveness was assumed to drop below a 42% decrease in pneumonia rates. The effectiveness of SDD has narrow confidence intervals (43 to 63%), so, in practice, this variation would probably not be realised. SDD also lost dominance if the base pneumonia rate was reduced. Chapter Three has illustrated the ranges in base ICU-acquired pneumonia rates. The implication of this sensitivity analysis is that the conclusions from this economic evaluation cannot be generalised to a particular unit, unless their base pneumonia rate is known.

The sensitivity analysis also demonstrated the effect of varying the economic parameters. The uncertainty around the increase in length of

ICU stay due to pneumonia and the costs associated with treating an episode of pneumonia was reflected in the wide ranges employed for sensitivity analysis. The more costly it was to treat an episode of pneumonia in terms of increased length of stay and increased intensity of treatment, the more likely SDD was to be dominant. SDD lost dominance if the increase in length of ICU stay was assumed to be less than 2.7 days. It also lost dominance if the cost associated with treating pneumonia was assumed to be less than £900.

The most precisely known resource use and associated unit costs were those of the SDD regimen. The sensitivity analysis showed that SDD remained dominant for all three regimens.

This analysis also identified the lack of long term outcome measures for intensive care patients. The hypothetical QoL model described in Chapter Three illustrated the areas where quality of life measurement is required. No work was found that examined the impact of ICU on long term quality of life or life expectancy. More specifically, no work was found that described the impact of iatrogenic events like ICU-acquired pneumonia on post-ICU recovery time, chronic health states and life expectancy. This type of investigation is essential to assess the impact of intervention on patient outcomes. There are no QoL tools designed for intensive care patients and no studies were found that used QoL tools to assess the impact of an intervention. In this analysis, the uncertainty around the LYGs and dQALYs gained did not affect the robustness of the conclusion that SDD was dominant. However, the estimates for LYGs and dQALYs gained were subject to wide variation, reflecting the uncertainty around the point estimates. Until research into the ultimate impact of ICU on quantity and quality of life is available, cost/LYG and cost/QALY ratios can only be very tentative.

4.6 CONCLUSIONS AND IMPLICATIONS FOR FURTHER ECONOMIC EVALUATION

This study has provided a framework for the economic evaluation of SDD. The secondary economic evaluation of SDD reported in this chapter has shown that SDD can be demonstrated to be economically dominant, given specified conditions. It has also shown that this conclusion is robust through wide ranges of the underlying clinical and economic parameters.

The sensitivity analysis showed that, although variations in effectiveness of SDD could reduce the robustness of the conclusions, this does not occur because the degree of uncertainty around effectiveness is known. However, variations in base pneumonia rate and the economic cost of an episode of pneumonia could also reduce the robustness of the conclusions, and do, as the degree of uncertainty around them is not known.

To improve the robustness of the conclusions, it is necessary to quantify the uncertainty around base pneumonia rates and the economic costs of treating a pneumonia episode. It is also necessary to obtain information on current practice patterns of SDD so that the assertion that the regimen used does not affect the robustness of conclusions can be confirmed with relevant practice information. The final recommendation from this evaluation is that evidence on the impact of ICU admission and ICU-acquired pneumonia on the morbidity and mortality of patients is also required. This is, unfortunately, outside the time scale of this project.

The epidemiological and economic evidence can be obtained in two ways. The first is to design an RCT of SDD that is powerful enough to detect differences in resource use and long term outcome attributable to

SDD. This provides a great deal of internal validity. However, the use of a clinical trial protocol decreases the external validity of the resource use data collected within it. RCTs essentially measure practice before the routine introduction of prophylaxis. Predictions of cost savings from a trial may not accurately reflect cost savings in clinical practice. Assessment of the difference in practice between clinical trials and clinical practice is necessary to make any economic evaluation generalisable. Therefore, some modelling would have to be carried out anyway. The second approach, therefore, is to pursue the decision-analytic model methodology used in the economic evaluation reported in this chapter. It is suggested that the availability of improved epidemiological and economic evidence will improve the robustness of the conclusions derived from this method without having to resort to an RCT.

Chapter 5: National Survey of Current Practice of SDD

5.1 INTRODUCTION

To carry out an economic evaluation of SDD in practice, it is necessary to have information about clinical practice, as it is probable that there will be significant deviations from the trial environment. Local circumstances have a bearing on efficiency. There is no published survey of patterns of SDD in clinical practice. This chapter reports the results of a national survey of the clinical practice of SDD in Britain.

Using a postal questionnaire, this survey reports on total numbers of centres, numbers and types of patients that receive SDD. SDD implementation and related practices in infection prevention such as stress ulcer prophylaxis policies, pneumonia diagnostic techniques and current antibiotic treatment of ICU-acquired pneumonia are investigated to build a more detailed picture of resource use in this area. The results provide an overview of the current state of dissemination of the therapy. Reasons for use or non-use of SDD are examined.

5.2 OBJECTIVES OF SURVEY

The aim of this survey was to determine current practice patterns relating to SDD.

The specific objectives were to determine:

1. which centres are using SDD in which patient groups;

2. the uniformity, or otherwise, of types of SDD treatments being used;

3. the prevailing opinions of clinicians regarding the efficacy of SDD and

4. which centres might be usefully contacted to obtain information about acquisition, compounding and administration costs of a range of SDD regimens.

Objectives 1 and 3 were addressed via a postal questionnaire to ICU clinicians. Objectives 2 and 4 were addressed via a postal questionnaire to ICU pharmacists.

5.3 METHODS

5.3.1 Study Design

As the primary objective of the study was to find out where and how SDD was being used, a postal questionnaire was the most appropriate survey method.

The questionnaire design was dictated by the need for a high return rate. This was required to provide the most accurate picture of clinical practice. Structured questions were employed to increase ease and speed of answering and to aid analysis. No assumption of knowledge of SDD was

made (Appendices 5.1 & 5.2).

The questionnaires and covering letters were designed with advice from a sociologist, two ICU clinicians, the microbiologist who designed SDD, Dr H. van Saene, and two ICU pharmacists.

Mostly factual information was to be obtained from the two questionnaires. This consisted of information on unit size and patient type; SDD implementation details and information on management of ICU-acquired pneumonia. Other information obtained from the questionnaire was concerned with clinicians' opinions about SDD. Number of patients treated per annum was omitted from the questionnaire and had to be ascertained by telephone.

The questionnaire was sent to all specified units in England, Wales and Scotland (273 ICUs).

5.3.2 Pilot Study

ICUs in Wales were identified from the Directory of Emergency and Special Care Units 1993 from the categories 'adult/paediatric intensive care unit' and 'intensive/coronary care unit'. A questionnaire was sent to ICU clinicians and ICU pharmacists at each hospital in the survey. Two postings were done. Telephone follow up was used to clarify points of detail. In the event of no response from a hospital at all, clinicians and pharmacists were followed up by telephone. The questionnaires were piloted in Wales in September and October 1993 (18 ICUs). Two postings of the questionnaire were employed, four weeks apart. The response rate after the first posting was 36.8% for clinicians and 72.2% for pharmacists.

For the second posting, the same questionnaire was sent to all non-respondents. After the second posting the clinician response rate was 68% and the pharmacist response rate was 94% (see Tables 5.1 and 5.2). The questionnaires were revised slightly to request more information from pharmacists and less from clinicians to improve clinician response rate. The questions on ulcer prophylaxis and antibiotic prophylaxis were transferred from the clinicians' to the pharmacists' questionnaire. Questions on status of responder were discarded from both questionnaires. The format of the questions was not altered, enabling the results from the pilot study to be used in the final analysis.

5.3.3 Main Study

ICUs in England and Scotland were identified from the Directory of Emergency and Special Care Units 1993 from the categories 'adult/paediatric intensive care unit' and 'intensive/coronary care unit'.The main study commenced in November 1993. 255 ICUs were included in the survey. The second posting was sent in December 1993. The same questionnaire was sent to all non-respondents. All centres that reported using SDD, via clinician, pharmacist or both were followed up in January 1994 by telephone for a variety of purposes. The number of patients treated with SDD in the previous year was obtained. Details of SDD regimens were clarified in a number of cases. Cost of SDD regimens was obtained from three centres.

5.4 RESULTS

5.4.1 Response Rate of Study

In the pilot study, 18 questionnaires were sent to clinicians and pharmacists. The clinician response rate was 68%, the pharmacist response rate was 94%, and one centre reported that there was no ICU present.

In the main study, a total of 255 questionnaires were sent to clinicians and pharmacists in England and Scotland (see Table 5.1). The clinician response rate was 69.8% and the pharmacist response rate was 82.8%. Eleven ICUs responded as having no ICU at the time of posting so were excluded from the analysis.

Table 5.1 Response Rate of Study

Questionnaires	Clinicians	Pharmacists
No. pilots sent	18	18
No. pilots returned	12	17
No. main study sent	255	255
No returned (1st & 2nd posting)	178 (133+45)	211 (134+77)
Total sent (pilot & main study)	273	273
Total returned (pilot & main study)	190	228
'No ICU present' reported	12	12
Final response rate (pilot study included, 'No ICU' excluded)	178/261 (68.2%)	216/261 (82.8%)

This resulted in a response rate from the 261 ICUs of England, Scotland and Wales of 68.2% (clinicians) and 82.8% (pharmacists). 57.9% ICUs returned responses from both clinicians and pharmacists. 10.3% ICUs responded via clinician only and 24.9% responded via pharmacist only. 6.5% centres did not respond via clinician or pharmacist.

All results discussed below include results of both the Welsh pilot study and the subsequent study in England and Scotland, unless stated otherwise.

5.4.3 Unit Characteristics

Mean reported annual ICU admissions was 371 (sd: 209, range: 70-1200).
Mean annual ICU surgical admissions was 205 (sd: 135, range: 0-900).
Mean annual ICU admissions staying for more than 3 days was 148 (sd: 81, range: 22-488). The National ICU audit carried out by the Royal College of Anaesthetists in 1992/3 for 254 ICUs in the United Kingdom reports that 43.3% patients stay on ICU for longer than 48 hours. This survey reports that 39.9% patients stay for longer than 3 days.

A comparison of unit characteristics for those ICUs using and not using SDD is reported in Table 5.2.

Table 5.2 Comparison of Characteristics of SDD Non-using and SDD-using ICUs

Unit Characteristics	Non SDD Users	SDD Users
Admissions p.a. Mean (sd)	367 (210)	435† (190)
Surgical admissions p.a. Mean (sd)	201 (135)	271† (135)
Admissions >3 days p.a. Mean (sd)	146 (80)	181 (81) ns

† $p<0.05$ (χ^2 test)

5.4.4 Extent of SDD Use

Clinicians or pharmacists from 16 centres reported using SDD. Centres using SDD and the regimens used is reported in Appendix 5.3. Twelve centres used the standard PTA SDD regimen as recommended by Stoutenbeek *et al* [1984]. This regimen consisted of an oral gel or paste (tobramycin 2%, amphotericin 2%, colistin 2%) and oral liquid (tobramycin 80mg, amphotericin 500mg, colistin 100mg) four times a day.

Two centres use gentamicin instead of tobramycin. One centre uses the liquid only. The two liver transplant centres use neomycin instead of tobramycin or gentamicin. This is the standard antibiotic used in liver transplant patients. Nine centres use SDD in ventilated patients and six centres use it in trauma patients. Adjunctive intravenous antibiotics are used by ten centres, nine of those using cefotaxime. According to the survey, the overall number of patients treated with SDD annually in England, Wales and Scotland is 530.

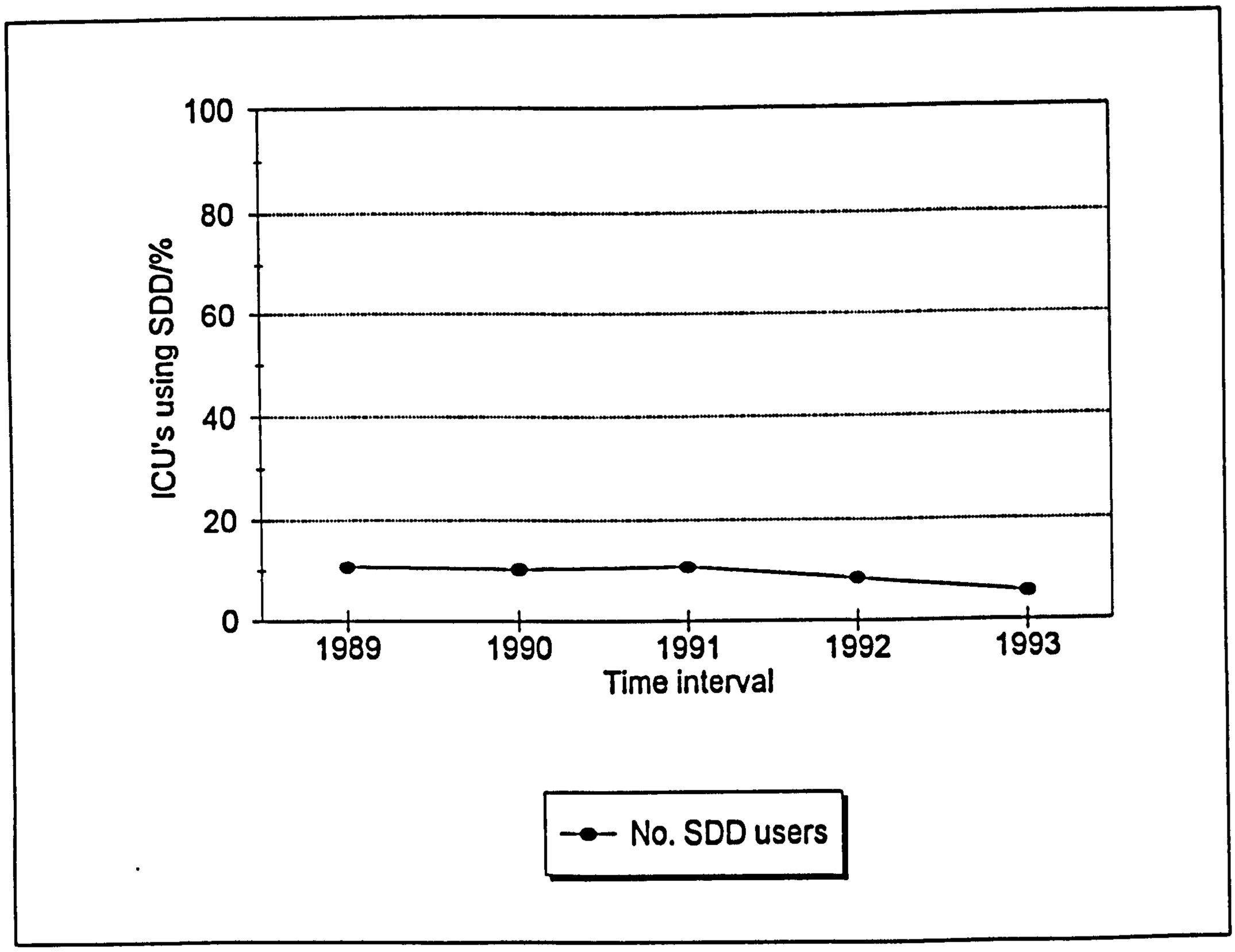
5.4.5 Cost of SDD Regimen

The constituents of the liquid and the intravenous antibiotics are available commercially, so costs will depend on local arrangements. The gel and paste are made by hospital pharmacy manufacturing units and sold to other hospitals. Two centres provided details of costs of making SDD paste or gel. None were able to give full breakdowns of cost, due to confidentiality, but provided costs per day of treatment that were reported to include drug acquisition costs and an element of manufacturing overheads. The paste and gel was reported to cost £1.30 and £4.50 per day, respectively.

5.4.6 Dynamics of SDD Use in Clinical Practice

The current ICU users of SDD reported the length of time that they have been using it. Figure 5.1 shows the trend in SDD use in ICUs in Britain from 1988 to 1993. In summary, of 44 ICUs in Britain that have implemented SDD over the last 5 years, 66% of centres have stopped using it.

Figure 5.1 Trends in SDD Use in ICUs In Britain (1988-1993)



5.4.7 Infection Control Related Practices

Clinicians at 16 ICUs reported using protected specimen brush technique to diagnose pneumonia. Most of these qualified their use of this diagnostic method as 'rare'. Stress ulcer prophylaxis at most ICUs consists of ranitidine and sucralfate as first line treatments (58.8% and 52.6%). Many centres reported using sucralfate as first line and only using ranitidine if nasogastric access was not possible. There was no significant difference between SDD users and non-SDD users.

Pharmacists from 211 ICUs reported the first, second and third line antibiotic regimens used on their unit to treat a suspected Gram negative infection before sensitivities are available. Pharmacists from seven ICUs reported no protocol. Pharmacists from 188 centres reported second line antibiotics and 147 centres reported third line antibiotics. Gentamicin is used most frequently, both alone and in combination at all three levels. It is most commonly used alone (65 reports) and in combination with piperacillin (20 reports), added to cefuroxime (15 reports), ceftazidime (13 reports) and ampicillin (11 reports). Apart from gentamicin, the most common first line antibiotic is cefotaxime (54/211 reports). The most commonly reported second line antibiotic is ceftazidime (42/188 reports). The most commonly reported third line antibiotic is ciprofloxacin (42/147 reports).

Clinicians from 72% of ICUs report monitoring infection rates (119 non-SDD users, 9 SDD users). Clinicians from 79% of ICUs report record severity of illness (130 non-SDD-users,10 SDD users). This compares with 122/256 (47.7%) centres reporting APACHE II scoring in the ICU Audit 1992/3. Five SDD users record SDD costs.

5.4.8 Clinicians' Opinions and Beliefs about SDD

This section examines the opinions and beliefs of ICU clinicians concerning SDD.

5.4.8.1 Clinicians' Opinions about SDD

Clinicians were asked to state whether they agreed with a range of

statements concerning the clinical efficacy of SDD. The results for ICU SDD-users (n = 11) and non-SDD users (n = 167) are summarised in Table 5.3. The only significant difference between the two groups was an increased belief by SDD users in the ability of SDD to reduce respiratory infection rate (p = 0.013). Most of both groups did not believe that SDD decreased mortality or length of stay, increased emergence of antibiotic resistant strains of bacteria or adherence to infection control policies.

Table 5.3 ICU Clinicians' Opinions Regarding the Clinical Efficacy of SDD

SDD efficacy parameters believed by clinicians	SDD Users n = 11	Non-SDD users n = 167
↓ Respiratory infections	9	72†
↓ ICU length of stay	2	11
↓ Mortality	2	16
↑ Antibiotic resistance	1	33
↑ Infection control policy adherence	3	27

†p = 0.013 (χ^2 test)

5.4.8.2 Clinicians' Reasons for Not Using SDD

Out of 167 non-SDD using clinicians, the most frequently reported reasons for not using SDD were lack of evidence for clinical efficacy (138 reports), financial and time constraints (46 and 49 reports), microbiological resistance (31 reports), pharmacy and nursing resistance, inappropriate

patients and not knowing about SDD (5 reports for each reason).

5.4.8.3 Clinicians' Knowledge About SDD

A postal questionnaire does not allow an in depth assessment of a clinician's knowledge base in SDD, upon which he bases his opinions. Awareness of the recent meta-analysis of 22 RCTs of SDD published in the British Medical Journal [1993] was used as proxy measure of clinicians' awareness of SDD and an indirect measure of their knowledge base. All clinicians using SDD reported reading the article, compared with 62.3% non-SDD users ($\chi^2 = 6.4232$, $p = 0.011$).

5.4.8.4 Comparison of Clinicians' Awareness of SDD with Their Beliefs About its Clinical Efficacy

The beliefs of non-SDD users about SDD's clinical efficacy were examined in relationship to their 'awareness' of SDD (Table 5.4).

Table 5.4 ICU Clinicians (Non SDD Users) Opinions Regarding the Clinical Efficacy of SDD and the Relationship with Awareness of SDD

SDD efficacy parameters believed by clinicians	Clinicians who had read SDD meta-analysis (n = 104)	Clinicians who had not read SDD meta-analysis (n = 63)
↓ Respiratory infections	53	19[1]
↓ ICU length of stay	7	4
↓ Mortality	12	4
↑ Antibiotic resistance	22	11
↑ Infection control policy adherence	21	6[1]

[1]$p < 0.001$

[1]$p = 0.07$

The results reported in Table 5.4 indicate that those clinicians who reported reading the SDD meta-analysis published in the British Medical Journal in 1993 have a more accurate knowledge of the areas of efficacy of SDD.

5.5 DISCUSSION OF RESULTS

This survey was sent to ICU clinicians and pharmacists to obtain information on current practice patterns of SDD. There was a high response rate, such that, of 261 ICUs, the SDD practice was known for 93.5%. Six clinician questionnaires were accidentally returned twice from the same centre, at least one month apart. This was due to overlap of the first and second postings. Five of the six questionnaires had been completed both times by the same clinician. The responses were virtually

identical from the first and second postings. This overall consistency between the first and second responses from these six centres suggests that the questionnaire was reliable.

This survey demonstrates that SDD is not being used in many centres around the country, and generally, a small number of patients at each centre receive the treatment (530 patients annually from 74,600 ICU admissions reported). Appropriate patient groups are being targeted, such as trauma and burns patients or those expected to be ventilated for more than 48 hours. These patients are those considered at high risk of nosocomial pneumonia and are most likely to benefit from SDD. Of the 44 ICUs reporting use of SDD, 66% have stopped using it.

ICUs that use SDD tend to have more annual admissions than non-SDD users, and a high proportion of these are surgical patients. The standard SDD regimens is most commonly used, 9 of the 16 centres using intravenous cefotaxime. Variations in regimens are mostly pragmatic in origin. The oral gel is more acceptable to the patient, but is more costly. The pastes and gels are not available commercially so are made by pharmacy manufacturing units who sell them to other hospitals. This resource use information, with the information on stress ulcer prophylaxis, pneumonia diagnosis and antibiotic treatment is necessary for economic evaluation of SDD in practice.

The other information obtained from this survey provides some insight into why SDD is not widely used in Britain. Measures of efficacy of SDD concentrate on decreases in pneumonias, mortality, length of stay, emergence of resistant bacteria and changes in infection control practices, with varying quality of evidence for each. SDD reduces incidence of pneumonias by 63% according to the recent meta-analysis of 22 RCTs

[SDD Trialists' Meta-Analysis, 1993]. There is no conclusive evidence that it reduces mortality or length of stay. There is no evidence that SDD increases the risk of emergence of resistant strains of bacteria [Stoutenbeek *et al*, 1987] or that SDD increases awareness of infection control in general. SDD users and non-users believed that SDD decreased pneumonias, and neither group tended to believe that it decreased mortality or length of stay, increased resistance or adherence to infection control policies. In summary, this means that the clinicians were largely basing their opinions of SDD on published evidence. A higher proportion of SDD users believed that SDD reduced pneumonias. This implies that clinicians are basing their opinions on clinical data available. However, the most commonly reported reason for not using SDD was lack of evidence of clinical efficacy. This may be due to lack of knowledge, or to a lack of confidence in the clinical data available. However, it is incongruent with this scepticism that the majority of technologies are used in the ICU setting without any effectiveness data at all.

A proxy variable for awareness or knowledge of SDD was employed by asking clinicians whether they recalled reading the SDD Trialists' meta-analysis in the British Medical Journal in 1993. Those who had not read the article were significantly less likely to believe that SDD reduced pneumonia incidence.

Clinicians may believe that SDD reduces pneumonia in the patient groups studied, but not in their own patients. Ten clinicians in the survey qualified their responses by stating that they did not believe that SDD would work in 'their patient population'. They also perceive it as a costly intervention, 27.5% responders reporting financial constraints as a reason for not using SDD.

5.6 CONCLUSIONS AND IMPLICATIONS FOR ECONOMIC EVALUATION OF SDD

The main aim of this survey was to provide resource use and unit cost information on SDD upon which to base an economic evaluation of SDD in practice. The information obtained includes number and type of patients, treatment schedules and some associated infection control practices. The numbers of patients reported as receiving SDD per year are probably estimates. They provide information on the order of numbers of patients receiving SDD each year. This allows the assessment of the current overall economic impact of SDD.

Economic evaluation of SDD in practice in a British ICU setting should therefore examine the use of the standard PTA regimen with cefotaxime in ventilated adult ICU admissions. This will provide an economic model that most closely mirrors current SDD practice patterns.

The secondary aim of the survey was to assess clinicians' opinions about SDD. If they are not using SDD because it is considered too costly, then an economic evaluation will affect their decision whether to use it or not. However, if they do not believe it is clinically effective, an economic evaluation is likely to have little impact on decision-making.

Chapter 6: Prospective Patient Cost and Outcome Study in Two British ICUs

6.1 INTRODUCTION

The secondary economic evaluation reported in Chapter Four identified a lack of evidence on the economic impact of ICU-acquired pneumonia and SDD implementation. This chapter describes a prospective observational study carried out at two British ICUs to obtain data on the economic impact of ICU-acquired pneumonia in two different practice settings, a London teaching hospital (LTH) and a district general hospital (DGH). Economic impact of ICU-acquired pneumonia, from the perspective of the ICU, can be determined by examining the difference in total patient costs attributable to an episode of pneumonia. Total patient cost is a function of length of stay and cost per patient day. Therefore, the cost parameters quantified by this study are total cost, length of ICU stay and cost per patient day.

Chapter Four also suggested that local factors including patient characteristics, ICU-acquired pneumonia rates and unit occupancy would affect the cost effectiveness of SDD. This study therefore provides data for these three categories.

The specific aims and objectives of the study are outlined in section 6.2. Section 6.3 describes the study design required to obtain data that fulfil these aims and objectives. Methods used for collecting resource use data and attaching costs to this information are outlined. The results of the study are reported in section 6.4. This section considers the proportion of

patients at each centre that would be appropriate for SDD therapy if it were implemented. These subgroups are examined separately to determine their admission characteristics, infection status, resource use and outcome. Finally, Section 6.5 discusses the study with reference to the strength of methods used, problems common to both centres and problems specific to each centre. The confidence with which the data collected can be used is discussed.

6.2 AIMS AND OBJECTIVES OF STUDY

The aim of this study was to identify and quantify the resource use associated with ICU-acquired pneumonia in a British ICU practice setting. This can be broken down into five specific objectives:

1. to obtain well-defined patient information on admission to ICU to allow characterisation of the populations studied;

2. to obtain bottom-up prospective resource use data and unit costs of that resource use to provide precise information on defined cost parameters (total cost, length of ICU stay and cost per patient day);

3. to obtain information on infection rates, using explicitly defined diagnosis criteria, to provide incidence rates for ICU-acquired pneumonia;

4. to obtain information on short and longer term outcomes of the populations studied and

5. to identify a patient group at the study centres that would have been suitable for SDD, if it were implemented at either centre.

6.3 STUDY DESIGN

This section describes the study designed to achieve the five objectives listed above. The four main areas of data required were patient admission characteristics, bottom-up resource use and associated costs, infection incidence rates and patient outcomes. The methods used, therefore, were designed to obtain these four groups of data. This section describes what information is required in each of these categories of data, why it is required and how it was collected. These data requirements dictate the remaining elements of the study design. These are the patient group size, patient inclusion criteria and selection of centres, also outlined in this section. Finally, the preliminary fieldwork and pilot study required to develop the methods used in the full study are reported.

6.3.1 Patient Admission Characteristics

Patient characteristics are required for four reasons. The first is to enable description of the study group in terms of severity of illness, diagnosis, age, chronic health, ventilation and infection status on admission, and type of surgery. The second is to assess the study group in terms of its generalisability to other ICU populations. For this reason, it is essential to use standard measurements of severity of illness and accepted diagnosis definitions. The third reason is to identify which patients in the study groups would be appropriate candidates for SDD therapy. This is required for the economic analysis in Chapter Eight. The fourth reason is that patient characteristics may have an impact on resource use. These characteristics need to be controlled for when assessing the impact of ICU-acquired pneumonia on resource use.

Therefore, the details collected for each patient on admission were those considered necessary to characterise the patient population and identify presence of risk factors for increased resource use. The parameters recorded are listed in Appendix 6.1a. Standard severity of illness scores (APACHE II) and diagnosis categories (APACHE II diagnosis categories [Knaus et al, 1985]) were used. Patients who would theoretically be considered suitable for SDD therapy are those ventilated on admission to the ICU, as discussed in Chapter Four. Therefore, the patient characteristics of this group are reported separately.

6.3.2 Cost Parameters and Resource Use Data

The second category of data required is the resource use associated with each patient and the cost associated with that resource use. This is required to quantify cost per patient and cost per patient day, required for use in the economic analysis of SDD. Total costs contain fixed, semi-fixed and variable components. As discussed in Chapter Two, total patient cost equates to the long run marginal cost of that patient. This is required to assess the long term impact of an intervention on ICU activity and capacity.

To be able to detect pneumonia-related changes in costs, patient-specific 'bottom-up' resource use data is necessary. Collection of this type of resource use data is labour intensive due to the evolving nature of hospital data retrieval systems in the UK. Therefore it is desirable to minimise this data collection by concentrating on resource use that is known to be affected, in this case by ICU-acquired pneumonia. However, it is not easy to assess which elements of resource use will be important at the outset, and which will not. Some resource use related to an infection like

pneumonia may be obvious, such as the use of antibiotics and microbiology tests. Other areas of change may not be so obvious, such as changes in artificial ventilation requirements or physiotherapy. Therefore, in this study, all identifiable resource use associated with a patient's ICU stay was recorded. The types of resource use collected are listed in Appendix 6.1b.

Once the resource use for each patient is known, costs need to attached to that resource use. The costs obtained should reflect the true economic cost of that service as closely as possible. Therefore, it was necessary that the source and components of those costs were known. If the full cost of a service was not known, then it was necessary to derive that cost prospectively. An example is the full cost of a drug dose including pharmacy department overheads and administration costs as well as the drug acquisition costs. It was necessary to be aware of all components of costs such that double-counting of costs was avoided, such as support department overheads. Table 6.1 summarises the source of fixed, semi-fixed and variable costs. The next sections describe the methods used for recording and costing fixed, semi-fixed and variable resource use.

Table 6.1 Sources of Fixed, Nursing (Semi-Fixed) and Intervention (Variable) Costs

Cost Category	Source of Costs
1. Fixed cost per patient/hour Estates, portering, electricity and lighting, laundry, cleaning, security, personnel, clinical engineering, management, finance, medical records, medical staff costs	Finance department
2. Nursing staff costs	Finance department
3. Intervention costs	
Chemical pathology tests	Chemical pathology department
Haematology and blood products acquisition costs administration disposables costs	Haematology department Contracts/supplies[1]
Interventions, ventilation, dialysis disposables costs drug costs	Contracts/supplies See 'drugs and nutrition'
Microbiology tests	Microbiology department
Drugs and nutrition drug acquisition costs administration disposables costs pharmacy department overheads	Pharmacy department Contracts/supplies Finance department
Physiotherapy treatment	Physiotherapy department
Radiology tests	Radiology department
Specialist beds	Intensive care contracts

[1]Intensive care contracts/supplies/central sterile supplies department

6.3.2.1 Fixed Costs

These are the costs that were incurred independently of ICU activity. They are costs of ICU to the estates department, electricity, security, laundry, cleaners, porters, catering, personnel, finance, management and clinical engineering. Fixed costs were obtained from the finance department of each hospital. The methods used to allocate the costs incurred from these departments were necessary to avoid double counting. They were allocated to each patient on the basis of a fixed cost per patient day.

6.3.2.2 Semi-Fixed Costs

In this study, semi-fixed costs referred to ICU nursing costs. The number of nurses and their grade on each shift was recorded. The cost to the hospital of employing each grade per hour was obtained. This allowed cost per shift to be calculated. Nursing cost per dependency point was used at LTH, as reported by Ridley *et al* [1991]. Dependency scores were not recorded at DGH so nursing costs were allocated by occupancy, not adjusted for dependency. Ridley *et al* [1991] also allocate medical staff costs on the basis of dependency scores, assuming that increased nursing dependence leads to increased clinician dependence. However, research by Dick *et al* [1992] demonstrates no significant relationship between nursing dependence and clinician dependence of ICU patients. This study therefore allocated medical staff costs as a fixed amount per patient day.

6.3.2.3 Variable Costs

Patient-specific resource use data were collected daily on an immediately

retrospective basis. The parameters recorded are listed in Appendix 6.1b. Interventions, such as intubation, and patient monitoring, such as ECG recording, were recorded at or soon after the time of occurrence. Resource use associated with those interventions and monitoring were obtained separately by observational study and interview. The associated cost of this resource use was obtained from relevant support and accounting departments.

6.3.3 Infection Status

SDD only reduces the incidence of a subset of ICU-acquired pneumonias, that is Gram-negative late-onset pneumonia. There is no evidence to suggest that management of different types of ICU-acquired pneumonias differs other than in the selection of antibiotics. Therefore, it is reasonable to assume that the resource use associated with Gram-negative late-onset pneumonia does not differ from ICU-acquired pneumonia in general. All episodes of ICU-acquired pneumonia experienced by patients were recorded. As other infections may also incur additional resource use, they were recorded. The patient's infective status was recorded from the patient's medical notes and from the microbiology department's records. Infections may be present on admission to ICU, or may be incurred during the patient's stay. During the ICU stay, infective episodes were recorded. Infections were categorized by site and type of organism. Site categories were abdomen, axilla, blood, central nervous system (CNS), groin, lines, lung, nasogastric aspirate, skin, stool, throat, vagina, urine and wound. Types of organism were Gram positive bacterial, Gram negative bacterial, anaerobic bacterial, fungal, viral and mixed. Major infections were classed as those originating in the abdomen, blood, CNS and lungs [Shulkin *et al*, 1993]. Other sites were classed as minor. Major infection episodes

treated without a positive microbiological culture ever being obtained were treated 'blindly', so were classed as 'blind' infections. Infection was defined as being present on ICU admission ('Pre-ICU'), becoming present in the first 48 hours of the ICU stay ('early onset') or becoming present after the first 48 hours of the ICU stay ('late onset'). *Gram-negative* late-onset pneumonia is the infection prevented by SDD. The incidence of Gram-negative late-onset pneumonia rates for patients hypothetically suitable for SDD (ventilated admissions) is required for the primary economic analysis.

Interview with ICU directors from both centres provided details of diagnosis of ICU-acquired pneumonia. At DGH, pneumonia was diagnosed by the clinical criteria of radiological changes or history of aspiration. At LTH, other clinical signs used were purulent sputum, deterioration in blood gases and temperature changes. Antibiotics were initiated before microbiological confirmation at both centres.

6.3.4 Patient Outcome

The impact of pneumonia on patient outcome ideally requires measurement of short and long term morbidity and mortality. Due to time constraints and the lack of QoL tools validated for use in this area, this study restricted itself to measuring outcome in terms of ICU, hospital and six month mortality. The least useful outcome measure is ICU mortality because moribund patients are often discharged to die privately on a ward. Hospital mortality is more useful, but does not reflect those patients who are discharged home or to a nursing home to die. The most useful short term mortality measure collected by this study was, therefore, six month mortality. Patients surviving beyond this time were much more likely to have recovered from the effects of their ICU stay. However, Ridley *et al*

[1994] have reported that mortality does not return to that of the normal population for up to four years after discharge. Unfortunately, this length of follow-up was beyond the scope of this study.

The patient's destination on leaving the ICU and hospital was recorded. This required telephone follow up at other hospitals in some cases. Six month mortality was recorded from hospital records, contacting the patient's GP or use of OPCS records.

The patient groups are examined in the analysis in Chapter Seven to assess whether factors such as which ICU a patient is admitted to, or ICU-acquired pneumonia, have an impact on mortality.

6.3.5 Patient Group Size

The principal statistical analysis method used in this study to identify resource use due to ICU-acquired pneumonia is linear regression analysis. This analysis technique demands that there are more observations than independent variables in the final linear regression model and that the difference between the two is as large as possible [Kennedy, 1993]. However, the determination of a specific sample size is not straightforward due to the nature of the linear regression model not being known prior to the analysis. The largest sample size possible within the experimental time frame should, therefore, be obtained.

6.3.6 Patient Inclusion Criteria

This section lists the criteria for selecting patients to include in the resource

use study. The selection criteria were used to exclude any patients that would not be considered to be 'true' intensive care patients. All consecutive adult ICU admissions (age 15 and above to allow collection of APACHE II scores) with lengths of stay of more than eight hours were included. A population of predominantly surgical patients was required, to provide a patient group hypothetically appropriate for SDD therapy. Lengths of stay of less than eight hours indicated patients not appropriate for ICU admission due to them being too well or their critical condition being irretrievable. Patients admitted because the CCU or HDU were full were excluded.

6.3.7 Selection of Centres

This section justifies the centres selected for the study. It was expected that ICUs in teaching hospitals and district general hospitals would have differing resource use patterns. Studies are often carried out in large teaching hospitals. It is not always clear that it is appropriate to generalize results from this setting to a district general hospital. To examine this potential difference, the study was carried out at two centres, LTH and DGH, with similar patient populations. The centres were selected by the following criteria:

1. appropriate patient population (adult, mostly surgical);
2. average or above average annual patient turnover (over 300 admissions [ICU Audit, 1992/93]);
3. relative ease of resource use data retrieval;
4. ethical committee and ICU director approval and
5. geographical convenience to enable three visits a week to each centre.

Both centres selected took trauma, post-general and vascular surgery patients. LTH also took neurosurgery patients. Centres using SDD were not used. This allowed easier isolation of resource use associated with ICU-acquired pneumonia, without the confounding effects of SDD on infection rates.

6.3.8 Preliminary Fieldwork and Pilot Study

The pilot study was carried out after preliminary fieldwork. This involved visiting the ICUs to identify what data could be collected routinely and from which sources. All support departments at each centre were visited to determine the most reliable data sources. In January 1994, a two week pilot study was carried out at both centres. The aims of this study were to:

1. determine that all required patient characteristic and resource use variables could be collected from both sites as planned and

2. determine which were the most reliable information sources.

The pilot study indicated that more data would be available from LTH. More detailed patient characteristics data were available due to the routine use of a patients admission database. This included daily collection of APACHE II scores, TISS scores and recording of interventions. APACHE II score on admission and daily TISS scores were available from DGH. All patient characteristic and resource use variables considered essential could be collected from both centres. Almost without exception, the most reliable source of variable resource use was the records of the clinical support service. A higher retrieval of resource use from LTH was expected

due to the higher degree of computerisation of clinical support records. Drugs, nutrition and blood products use were recorded from bedside charts. Interventions, line and drain changes were recorded from notes and from the attending nurse. At LTH, physiotherapy time was recorded as the quantity of 15 minute treatment sessions for each day. This was not carried out at DGH, the physiotherapist recording a visit on the patient's chart only.

6.3.9 The Full Study

The study was passed by the Ethics Committees at both hospitals. Each required that the patients included in the study give their signed consent. Patient recruitment for the full study was carried out at both centres from 1st February 1994 to 30th November 1994. Data collection was continued until all recruited patients had been discharged from the ICUs.

6.4 RESULTS

This section reports the results of the resource use study. The results of this study are divided into three sections:

1. patient admission, infection and outcome characteristics;
2. costs associated with resource use obtained from each centre and
3. patient resource use characteristics.

6.4.1 Patient Population Characteristics

This section summarizes the patient admission, infection and outcome characteristics for the study groups obtained from the two centres.

At LTH, 237 admissions were recorded for 224 patients. There were 212 eligible first admissions. In accordance with the study inclusion criteria, 12 admissions were excluded as the patients were on ICU for less than 8 hours. Thirteen admissions were readmissions. At DGH, 189 admissions were recorded for 170 patients. There were 137 eligible first admissions. In accordance with the study inclusion criteria, 52 admissions were rejected (19 readmissions (10 for haemodialysis sessions), 24 less than 8 hours long, 6 CCU overflow patients and 2 patients younger than 15 years old).

6.4.1.1 Patient Admission Characteristics

No patient refused to be entered into the study. Table 6.2 summarises characteristics of eligible first admissions at both centres. The populations are similar in their age, sex and severity of illness distribution. Mean patient age and APACHE II score are similar to those reported by other British ICUs [Shiell, 1989; Ridley *et al*, 1993]. Both centres have a predominantly surgical population, although the proportion of surgical patients is higher at LTH. Table 6.3 illustrates the similar profile of surgical specialities at the two centres. The difference worthy of note is that LTH ICU takes neurosurgery patients because the hospital is a tertiary referral centre. LTH is also a tertiary referral centre for oncology, reflected in the higher proportion of admissions with active cancer. There were many reasons for admission recorded by the clinicians at the two centres. The

largest groups at both centres were 'post peripheral vascular surgery' (21% at DGH; 16.5% at LTH), 'post neurosurgery' at LTH (12.3%) and 'respiratory insufficiency post-op' (17.4% at DGH, 9.0% at LTH). All recorded categories are detailed in Appendix 6.2. The patients at the two centres have similar types of previous medical history, levels of infections on admission, cardiopulmonary resuscitation prior to admission and subsequent readmissions to ICU. LTH has a substantially higher unit and hospital mortality than DGH. Reasons for this are examined in Chapter Seven. The mean ICU and hospital mortalities reported by Metcalfe *et al* [1995] for 257 British ICUs were 18% (range:4 to 41%) and 26% (range 10 to 50%) respectively. The mortalities reported here fall within these ranges. A major proportion of admissions to both centres were ventilated. These patients are those hypothetically suitable for SDD therapy. These patient groups are examined separately in section 6.5.6.

Table 6.2 Summary of Eligible Patient Characteristics (First admission only)

Patient characteristic	DGH (n = 137)	LTH (n = 212)
Age[1]	61.1; 16.4; 15-91; 62.8	59.3; 18.3; 15-90; 63.1
Sex (% male)	60.6	56.6
APACHE II[1]	15.0; 7.7; 0-40; 14.0[2]	14.7; 7.0; 3-44; 14[3]
% Surgical	63.5	76.4
% Elective	32.8	34.9
% reported PMH	67.4	54.7
% Active cancer	10.9	27.8
% Infected admissions	26.3	24.1
% CPR before ICU	8.8	8.0
% admitted ventilated	65.0	80.7
% ventilated on ICU	67.9	86.8
% dialysed	7.3	11.3
% with a PA catheter	30.7	33.0
% Readmitted	6.1	6.5
% ICU mortality	13.1	24.5
% Hospital mortality	28.5	36.7
% 6 month mortality	35.9[4]	45.6[5]

[1] Mean, sd, range, median

[2] n = 130 as there are 7 missing values; [3] n = 207 as there are 5 missing values

[4] n = 131 as there are 6 missing values; [5] n = 206 as there are 6 missing values

Table 6.3 Distribution of Surgical Admissions

Type of Surgery	DGH (%)	LTH (%)
No surgery (medical)	50 (36.5)[1]	50 (23.6)[2]
General surgery	36 (26.1)	49 (23.1)
Vascular surgery	35 (25.4)	43 (20.3)
Neurosurgery	0 (0)	38 (17.9)
Trauma surgery	2 (1.5)	10 (4.7)
Other surgery	14 (10.1)[3]	22 (10.4)[4]

[1] Cardiology, general medicine, geriatrics, nephrology, neurology and paediatrics.

[2] Cardiology, general medicine, geriatrics, haematology, nephrology, neurology, oncology and rheumatology.

[3] Gynaecology, orthopaedics, plastic surgery and urology.

[4] ENT, orthopaedics, plastic surgery and urology.

6.4.1.2 Infection Status of Patients

The infection status of patients was recorded on admission to ICU and monitored throughout the ICU stay. This provided the incidence rate of serious infections and specifically pneumonia. These were divided into 'Pre-ICU', early onset and late onset infection rates. Tables 6.4a and 6.4b detail the incidence of serious infections and pneumonias that occurred on the two ICUs. Not all infections and pneumonias were confirmed by a microbiological culture, but were treated on the basis of clinical criteria. Infections that were treated in this way are termed 'blindly treated'. The incidence of infections including these blindly treated infections are included in the tables in parentheses. 'Pre-ICU' infections were those that

had been diagnosed and where treatment had been initiated prior to ICU admission. Early and late-onset infections are diagnosed and treated after ICU admission. Identification of resource use associated with ICU-acquired pneumonia examines the two latter groups together.

Table 6.4a Incidence (Number of Episodes per Patient) of Serious Infection and Pneumonia Episodes in Eligible First Admissions at LTH (n = 212)

Infection category	Pre-ICU[2]	Early onset[2]	Late onset[2]
Serious infection[1]	0.24 (0.24)	0.14 (0.21)	0.70 (0.76)
Pneumonia	0.09 (0.09)	0.07 (0.14)	0.42 (0.48)[3]

[1] Includes pneumonia, CNS, abdominal sepsis and bloodstream infection.

[2] Infections with and without positive microbiological culture in parentheses

[3] 102 episodes of late-onset pneumonia in 65 patients (63% are Gram-negative, so the incidence of Gram-negative late-onset pneumonia is 0.30 episodes per ICU admission).

Table 6.4b Incidence (Number of Episodes per Patient) of Serious Infection and Pneumonia Episodes in Eligible First Admissions at DGH (n = 137)

Infection category	Pre-ICU[2]	Early onset[2]	Late onset[2]
Serious infection[1]	0.27 (0.27)	0.14 (0.26)	0.11 (0.16)
Pneumonia	0.18 (0.18)	0.06 (0.18)	0.09 (0.15)[3]

[1] Includes pneumonia, CNS, abdominal sepsis and bloodstream infection.

[2] Infections with and without positive microbiological culture in parenthesis

[3] 20 episodes late-onset pneumonia in 18 patients. (60% are Gram-negative, so the incidence of Gram-negative late-onset pneumonia is 0.09 episodes per ICU admission).

The overall ICU-acquired serious infection and pneumonia rates recorded at the two centres are very different, 97% and 62% respectively at LTH compared with 42% and 33% respectively at DGH. These infection rates, reflect the range of incidence rates discussed in Chapter Three. A recent epidemiological study of ICU-acquired pneumonia in British ICUs confirms that, while the incidences observed here are very different, they merely reflect the wide range reported around the country [Vincent *et al*, 1995]. The high proportion of ICU-acquired serious infection that is pneumonia observed here is reflected in the published evidence reported in Chapter Three. The higher incidences of ICU-acquired pneumonias on large surgical ICUs was also reported by George *et al* [1993].

The ICU-acquired and Gram-negative late-onset pneumonia rates for ventilated patients are reported separately in section 6.5.6.

6.4.2 Summary of Costs Associated with Resource Use Obtained from each Centre

This section reports the sources and components of costs associated with resource use obtained from each of the study centres. Fixed, semi-fixed and variable costs are reported.

6.4.2.1 Fixed Costs

The fixed costs allocated to the ICU at each study centre are reported in this section. Departmental overheads were allocated using locally designed allocation models. Local allocation of overheads is detailed in Table 6.5. At both centres, intensive care was categorized as a clinical support service. Therefore, other clinical support services were not allocated to ICU as all clinical support services were allocated directly to clinical directorates. A range of allocation methods were used, such as the allocation of costs on the basis of floor area, bed days, staff time and workload.

This study apportioned fixed costs to individual patients according to their length of stay on the ICU, to the nearest half hour. The fixed cost per patient day was derived for both centres using total fixed costs for the year and total patient days during that time period. At LTH, total patient days on ICU for 1994/95 was 1830. This gives a fixed cost per patient day of £129.1. At DGH, total patient days for 1994/95 were derived from the dataset as 1100 per annum, giving a fixed cost per patient day of £182.6.

Table 6.5 Department overhead costs and methods (1994/5 budget)

Department	DGH cost p.a./£	LTH cost p.a./£	Method of allocation
Estates Portering and waste Security Catering Sewing room	20656 4140 760 4849 2049	21191 5224 970 - -	Floor area
Cleaning	29600	37466	hours/week
CSSD[1]	7747	24207	Issues
Supplies department	29782	38869	Pro rata to cost of issues
Telecommunications	8512	14093	Workload
Personnel Occupational health Staff dental Human resources Nursing education Finance	9979 - - 5270 37075 15873	- 3679 255 4890 0 29328	WTE's[2]: 58.2
Executive services and senior management	24611	5319	Pro rata to other overheads
Pathology Imaging services Physiotherapy	0 0 0	0 0 0	Overheads in request costs
Pharmacy (non drugs) Clinical engineering	(80000)[3]	(86955)[3] 50777	6.27% of workload 6.51% of workload
TOTAL departmental overhead allocation:	200903	236268	

[1] Central Sterile Supplies Department

[2] Whole time equivalents

[3] Not included in this total, added to drugs *pro rata*

6.4.2.2 Nursing and Medical Staff Costs

This section reports the allocation of medical and nursing staff costs to patients at the two centres. To do this, it was necessary to determine total nursing and medical costs for each unit and allocate costs appropriately to each patient. Total nursing cost per shift was obtained by recording the number and grades of permanent and temporary nursing staff present for each shift from the nursing duty rota. The cost to the hospital of employing each nursing grade for a shift was obtained from finance departments. Costs of temporary nursing staff were obtained from the Clinical Nurse Leader, derived from the 1994/95 financial year. Costs included the nurse's wage, inner or outer London allowances and hospital employer contributions. The grades of nurse ranged from 'D' to 'H'. The cost for the midscale of each grade was used. Shifts were costed according to the number of hours they lasted and whether they occurred on weekdays, weekends or bank holidays. Appendix 6.3 summarises costs per shift for each grade at both centres. Total nursing cost per shift was then derived. The simplest allocation method is the use of ICU occupancy to derive nursing cost per patient day (see Table 6.6).

Table 6.6 Summary Statistics of Nursing Cost per Patient Day (calculated from data from 271 days)

Cost per patient day/£	DGH	LTH
Mean	332.4	307.0
Standard deviation	148.5	65.9
Median	246.64	287.8
Range	151.6-939.9	201.1-743.0

Nursing costs per shift varied quite widely, due to usual staffing problems such as people calling in sick and not being able to employ bank or agency staff. Senior staff were sometimes all on the same shift to enable management meetings to be carried out. These variations were due to factors other than the patient occupancy. To eliminate their effect on individual patient costs, mean nursing costs per patient day were used. Table 6.6 shows that the two centres had similar nursing costs per patient day. The increased variation at DGH is a function of the smaller ICU size. A unit change in patient occupancy has a larger proportional effect on cost per patient day in a smaller ICU. The occupancy *of staffed beds* at LTH and DGH for the study period was 93.5% (range 88.4% to 97.7%) and 69% (range not reported) respectively. The mean monthly patient refusal rate at LTH was 44% (range 26% to 65%) (see Chapter Two for definitions of patient refusal rates). This meant that for every 100 admission requests, 44 were refused. This may have included one patient being refused more than once. Refusal rates were not recorded at DGH.

At LTH, routine recording of ICS dependency scores enabled allocation of

nursing costs by patient dependency. To derive the nursing cost associated with each patient per shift, the total nursing cost per shift was allocated to patients according to nursing dependency (Appendix 2.2). This is the method reported by Ridley *et al* [1991]. The sum of individual patient dependency scores was the total shift dependency score. Nursing cost per dependency point for each shift was calculated (see Table 6.7). Mean cost per dependency point for early, late and night shifts were used. This allowed the daily nursing cost for each patient to be derived, depending on their nursing dependency scores.

Table 6.7 Summary Statistics of Nursing Cost per Dependency Point for Early, Late and Night Shifts at LTH (calculated from data from 341 days)

Parameter	Early Shift	Late shift	Night Shift
Mean cost per dependency point	67.83	62.94	92.46
Standard deviation	18.77	15.92	22.23
Median	64.77	60.17	87.92
Range	36.02-148.06	33.36-126.16	52.98-185.38

Although nursing costs were allocated at LTH using the ICS dependency scoring system, the correlation between patient nursing costs and length of ICU stay was 0.991. This indicates that nursing costs were virtually behaving as a fixed cost.

Details of medical staffing levels on the ICU were obtained from Clinical

Directors. Medical staff costs were obtained from finance departments (see Appendix 6.4). Total medical costs were derived for each centre and allocated to each patient according to their length of stay on the ICU. Medical costs per patient day were £132 at LTH and £124 at DGH.

6.4.2.3 Variable Costs

The resource use associated with each patient was recorded as described in section 6.3.2. Acquisition of costs attached to each area of resource use is described in this section. The areas of resource use costed were pathology, radiology, drugs and nutrition, monitoring and interventions whilst on the ICU.

6.4.2.3.1 Pathology Tests (Chemical pathology, haematology, microbiology)

At both centres, pathology departments provided components and sources of costs. This involved annuitised and discounted fixed costs being combined with variable and staff costs to combine an overall cost for the financial year 1994/95. Costs of blood products provided included the acquisition cost only. Costs of 48 chemical pathology, 17 haematology (and 4 blood products) and 29 microbiology tests were obtained from LTH and 30 chemical pathology, 9 haematology (and 4 blood products) and 23 microbiology tests were obtained from DGH.

6.4.2.3.2 Radiology Tests

Radiology departments provide a range of imaging services from 'X-rays' of

all parts of the body, to ultrasound examinations of internal organs, computerised tomography (CT) scans of the head and spine, magnetic resonance imaging (MRI) scans of the head and body. Due to their immobile and unstable condition, ICU patients are not able to be transported to the department so the radiology department uses portable machines to provide X-rays and ultrasound scans on the ICU. The radiology department also provided the sources and components of the costs of their tests. This involved annuitised and discounted fixed costs being combined with variable and staff costs to combine an overall cost for the financial year 1994/95. Costs of 38 radiology investigations were obtained for LTH and 12 for DGH.

6.4.2.3.3 Drugs and Nutrition

The pharmacy department provides drugs and nutritional products to ICU at both centres. Only acquisition costs of products were available from the pharmacy department. It was necessary to construct costs of doses by including the acquisition cost of the drug with a pharmacy overhead cost and costs of disposables required to prepare the drug for administration. Pharmacy annual running costs excluding drugs costs were obtained from the finance department. The pharmacy overhead cost per individually dispensed item was derived as £1.10 at LTH and £1.48 for DGH. Details of intravenous fluids and disposables required to prepare the drug for administration were obtained from hospital policies, observation and interview with nursing and pharmacy staff. Appendix 6.5 details the derivation of the overhead cost and provides illustrations of drug cost breakdowns. Costs for 200 drugs (antibiotics, cardiac drugs, respiratory drugs, sedatives, plasma expanders and miscellaneous other drugs) and nutrition products were constructed in this way for both centres.

6.4.2.3.4 Monitoring and Interventions on ICU

Information regarding resource use associated with respiratory therapy, physiotherapy, line and drain insertion and maintenance, use of special beds, renal replacement, patient monitoring and other interventions such as post mortem care was obtained by observation and interview. Costs associated with resource use were obtained from the NHS supplies catalogue, supplies department, central sterile supplies department, physiotherapy department and individual contract arrangements. All costs were obtained for the financial year 1994/95 and included V.A.T. Appendix 6.6 details the interventions for which resource use details were obtained, sources of costs and illustrations of cost construction for interventions.

These costs were attached to the resource use recorded for each patient, to derive total patient costs and cost per patient day.

6.4.3 Individual Patient Resource Use and Costs

This section reports the values for the cost parameters previously outlined in section 6.2.1 for the patient groups at each centre. The mean, median and 95% confidence intervals for total costs, total variable costs, length of ICU stay, total cost per patient day and variable cost per patient day are reported. The constituents of total costs are reported. The frequency distribution of the cost parameters is reported and the relationship between total costs and length of ICU stay is demonstrated.

6.4.3.1 Summary of Results for All Eligible First Admissions

The mean total cost, variable cost, total cost and variable cost per patient day and length of ICU stay of eligible first admissions is reported in Table 6.8. LTH has a higher mean cost per patient and a much higher variable cost per patient than DGH. The mean length of ICU stay is similar for the two centres. This results in the cost per patient day and variable cost per patient day being higher at LTH than at DGH. The mean total cost per patient day at LTH derived in this study correlates closely with the top-down patient day cost supplied by the LTH finance department for the financial year 1994/95 of £1100. This information was not available at DGH. At both centres, the distribution of total cost, variable cost per patient and length of stay is heavily skewed by high cost outliers, as indicated by the differences between median and mean. This non-normal distribution of these parameters is illustrated in Figures 6.1 and 6.2. Variable cost per patient showed a similar distribution to total cost per patient as illustrated in Figure 6.1. Cost per patient day is much more normally distributed, suggesting a relatively constant treatment intensity between patients. This is illustrated in Figure 6.3. Variable cost per patient day shows a similar distribution. The plots in Figures 6.1 and 6.2 suggest that total patient costs are highly correlated with length of ICU stay. At LTH, total costs and variable costs per patient are highly correlated with ICU length of stay (Spearman $\rho = 0.983$, 0.946 respectively). This close relationship is illustrated by the scatter plots in Figure 6.4. The linear fit to the observed data shows a very close relationship, even at the longer lengths of ICU stay. At DGH, total costs and variable costs per patient were less closely correlated with ICU length of stay ($\rho = 0.551$, 0.543 respectively). This lower level of correlation is illustrated by the scatter plots and linear fit in Figure 6.5. The reasons for this difference in relationship are discussed in section 6.5.3.

Table 6.8 Cost per Patient, Length of ICU Stay and Cost per Patient/day of All Eligible First Admissions

Cost parameter: Mean (95% CI of mean, range, median)	DGH/£	LTH/£
Total cost per patient	5204.9 (3820.9-6588.9, 332.3-59288.4, 1836.7)	7288.2 (5766.8-8809.6, 316.2-82053.7, 2746.3)
Variable cost per patient	1729.6 (1173.5-2285.7, 49.8-28144.6, 532.5)	3304.5 (2602.5-4006.5, 101.1-39017.2, 1276.9)
Length of ICU stay	5.36 (4.03-6.69, 0.33-48.73, 2.04)	6.83 (5.44-8.22, 0.44-66.45, 2.80)
Total cost per patient day[1]	945.6 (911.8-979.4, 681.6-1728.7, 888.0)	1099.2 (1050.2-1148.2, 643.2-3021.6, 1003.2)
Variable cost per patient day[1]	307.2 (273.4-341.0, 42.48-1089.6, 248.2)	520.8 (475.7-565.9, 157.0-2170.6, 430.8)

[1]Costs per patient hour were calculated, and then converted to a cost per patient day.

Figure 6.1 Frequency Distribution of Total ICU Patient Cost (Eligible First Admissions at LTH and DGH)

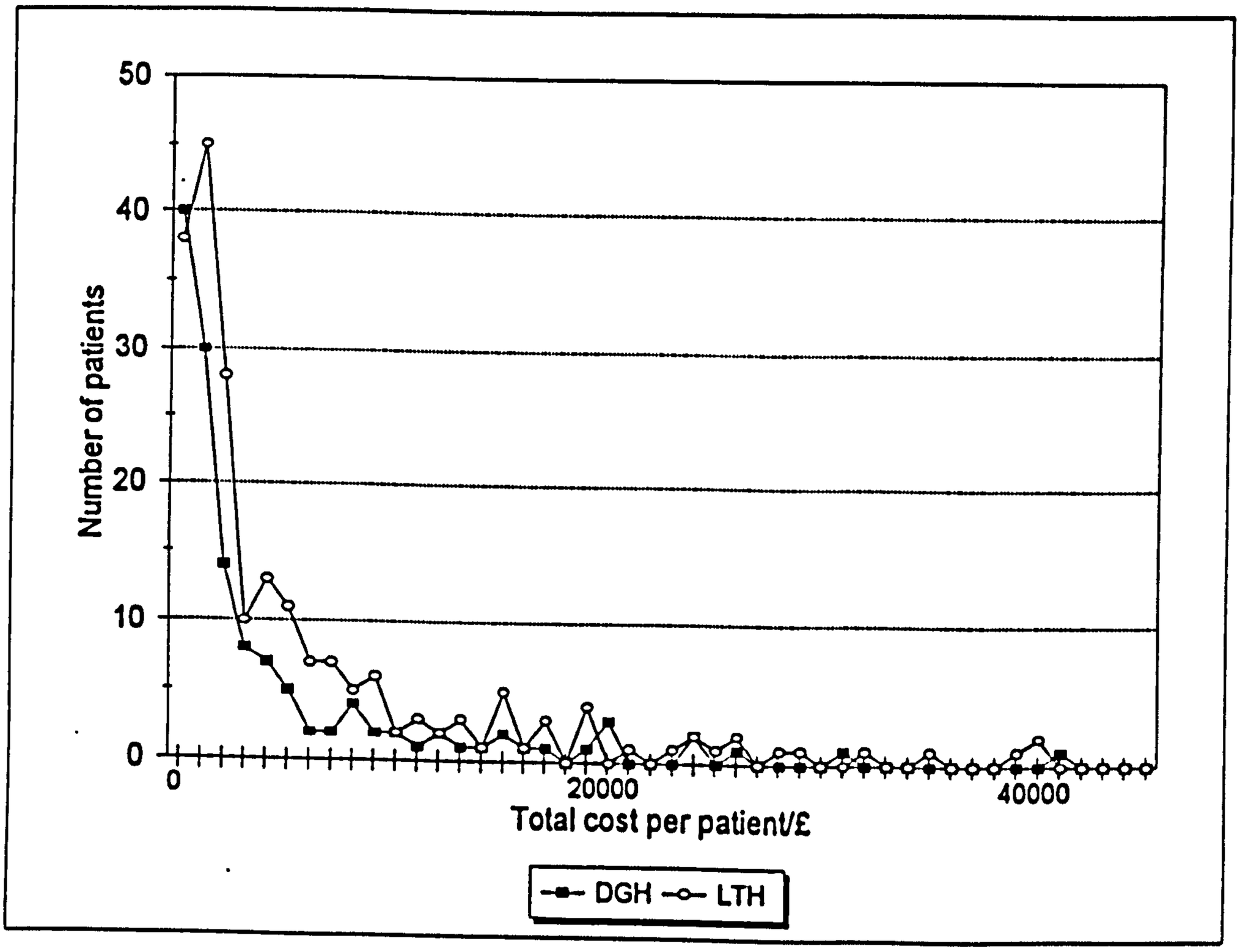


Figure 6.2 Frequency Distribution of ICU Patient Length of ICU Stay (Eligible First Admissions at LTH and DGH)

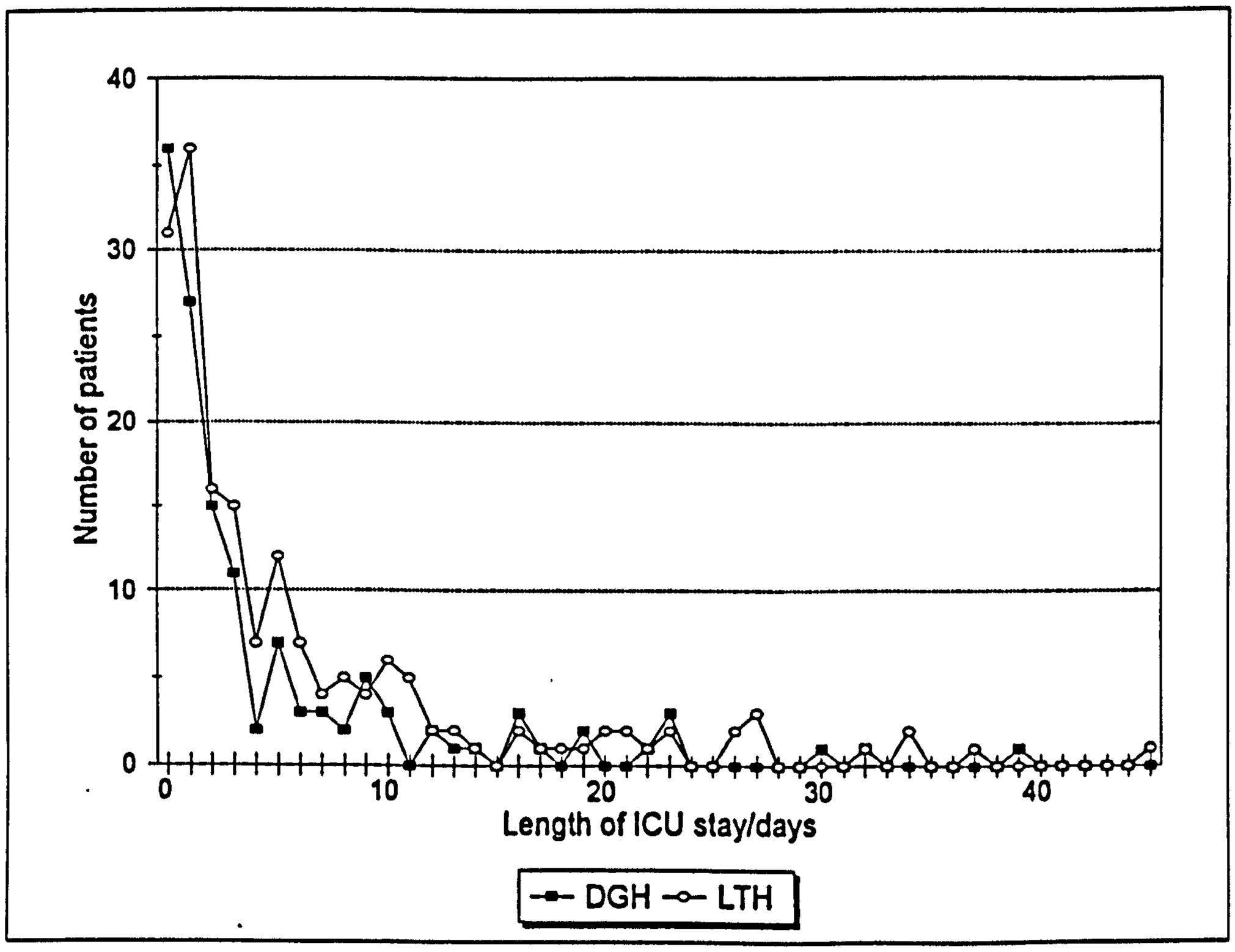


Figure 6.3 Frequency Distribution of ICU Patient Cost per Patient Day (Eligible First Admissions at LTH and DGH)

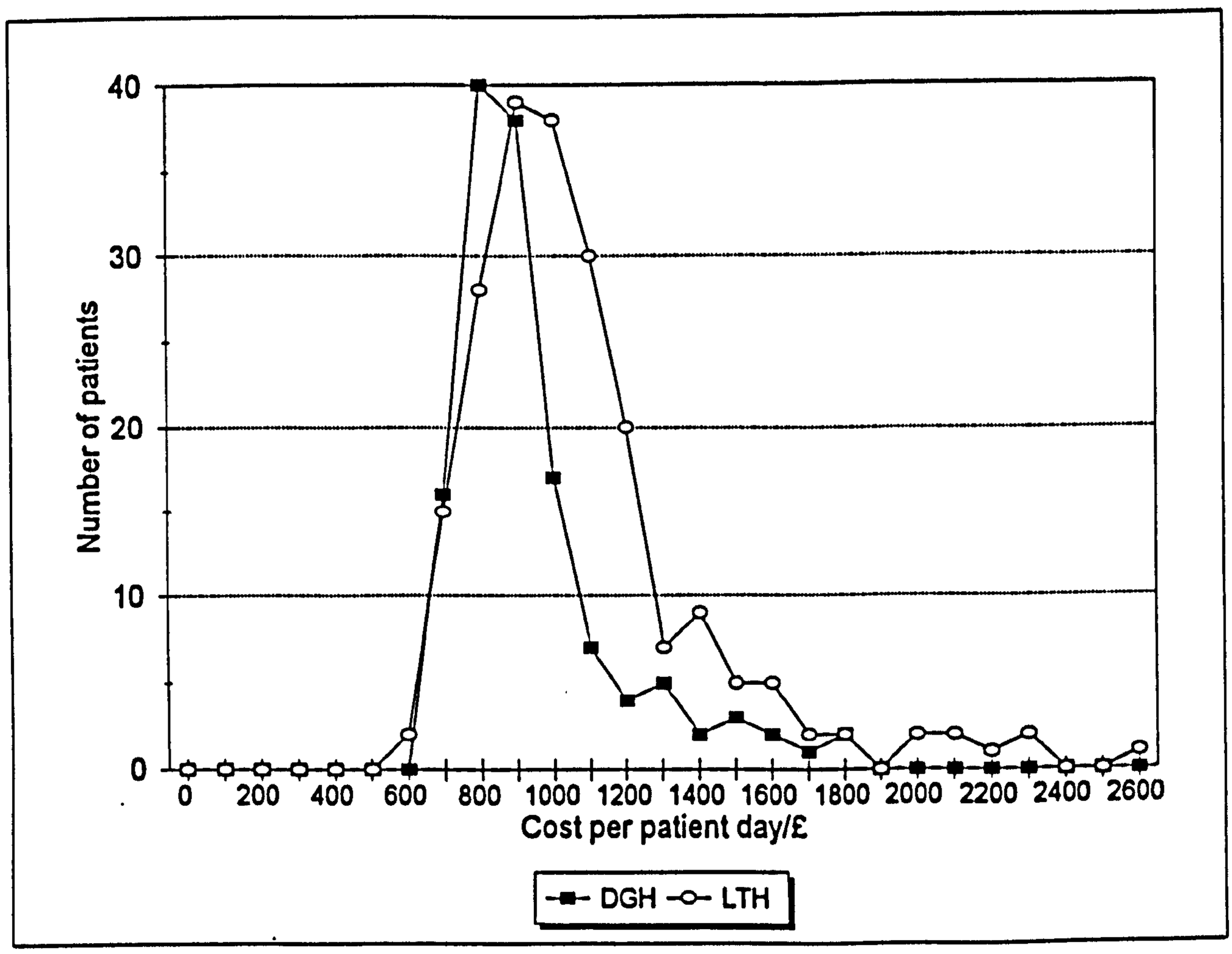


Figure 6.4 Relationship of Total Patient Cost with Length of ICU Stay (Eligible First Admissions at LTH)

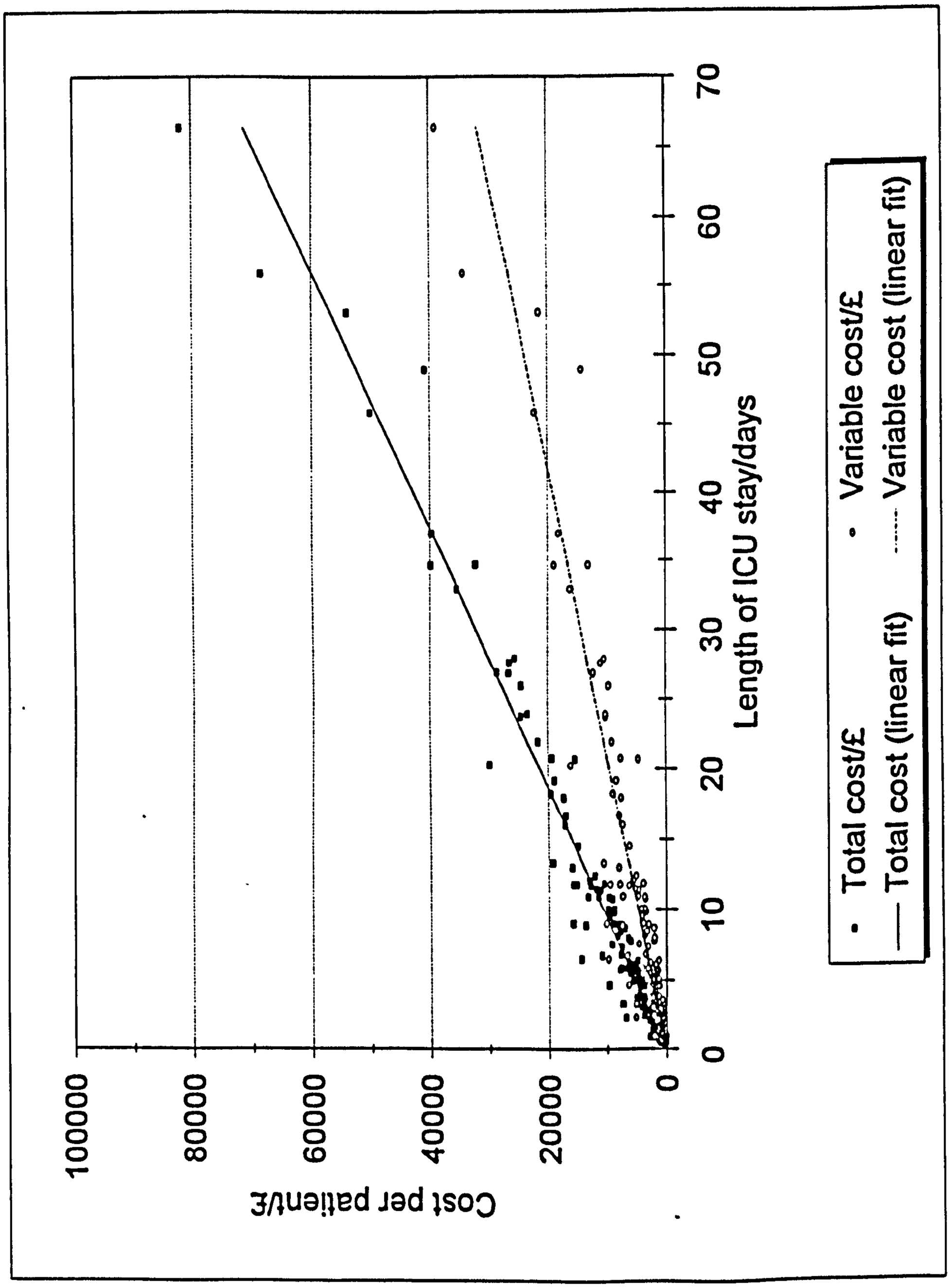
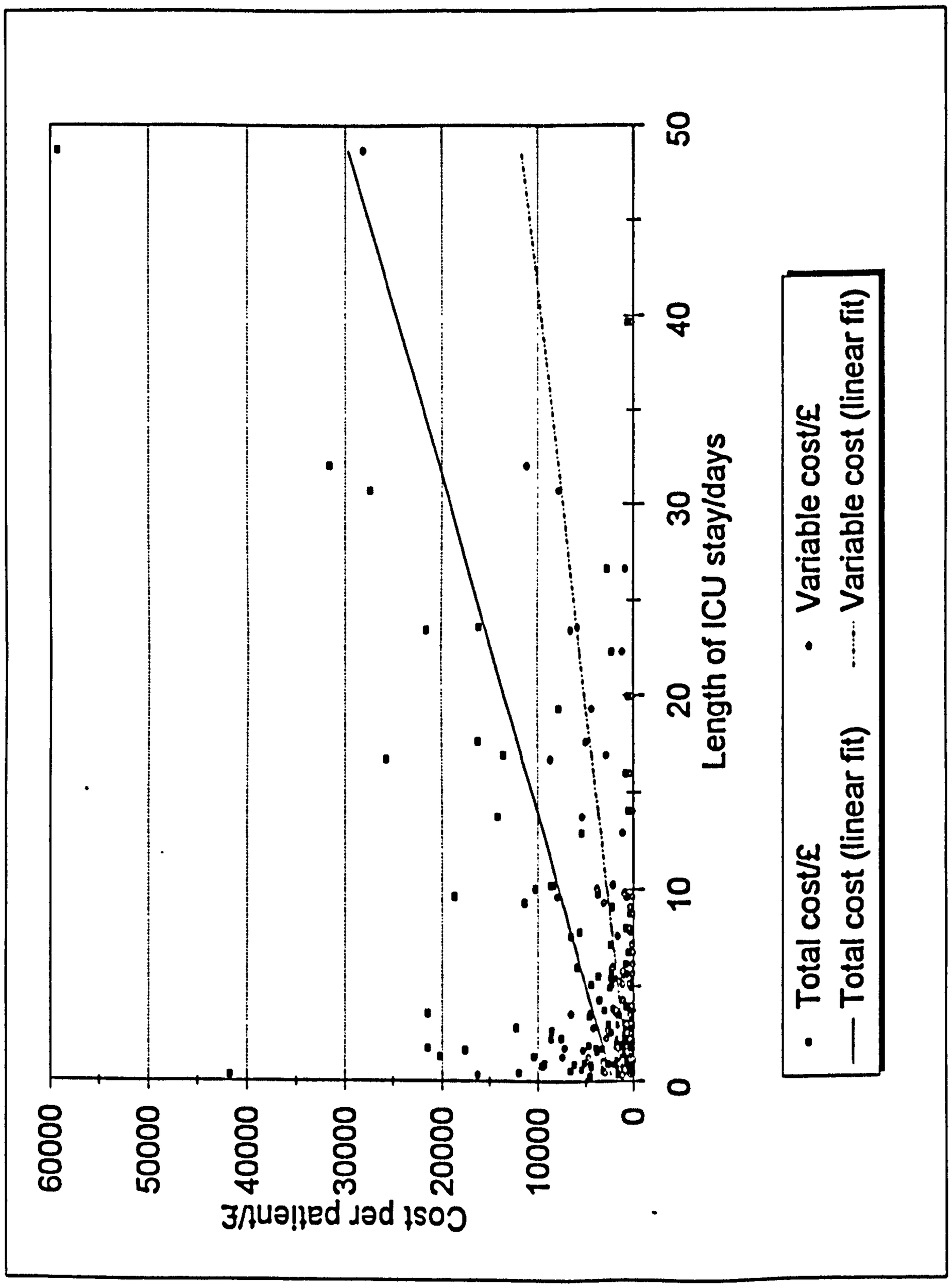


Figure 6.5 Relationship of Total Patient Cost with Length of ICU Stay (Eligible First Admissions at DGH)



The components of total patient costs is reported in Table 6.9. The increased total patient cost at LTH is due to an increased nursing, medical and variable cost. Most areas of variable cost are higher at LTH. The five principal areas of variable cost that appear to contribute to higher costs at LTH are use of blood products and drugs, radiology, physiotherapy and the use of special beds. Reasons for this are discussed in section 6.5.3.

Table 6.9 Components of Total Patient Costs (Eligible First Admissions)

Cost component	Cost at DGH/£ (%)	Cost at LTH/£ (%)
Fixed overheads	993.1 (19.1)	880.7 (12.1)
Staff:		
Nursing	1807.5 (34.7)	2202.6 (30.2)
Medical	674.7 (13.0)	900.5 (12.4)
Variable Total	1729.6 (33.2)	3304.5 (45.3)
Blood products	426.6 (8.2)	991.9 (13.6)
Drugs	459.6 (8.8)	626.2 (8.9)
Radiology	72.5 (1.4)	453.2 (6.2)
Physiotherapy	179.3 (3.4)	309.2 (4.2)
Respiratory therapy	160.6 (3.1)	158.0 (2.2)
Haematology	69.7 (1.3)	141.1 (1.9)
Special beds	0 (0)	129.1 (1.8)
Renal therapy	89.8 (1.7)	133.5 (1.8)
Microbiology	41.5 (0.8)	98.4 (1.4)
Chemical pathology	65.9 (1.3)	100.4 (1.4)
Lines	54.0 (1.0)	84.7 (1.2)
Monitoring	17.4 (0.3)	34.8 (0.5)
Nutrition	88.6 (1.7)	20.2 (0.3)
Drains	2.1 (0.1)	20.6 (0.3)
Other events	1.9 (0.1)	3.0 (0.0)
Total	5204.9	7288.2

6.4.3.2 Epidemiological and Economic Parameters of Patients Suitable for SDD at the Two Centres

This section summarises the epidemiological and economic cost parameters of the patient groups hypothetically considered suitable for SDD at both centres. In the economic analysis of SDD, ventilated admissions from the two study centres are the hypothetical target patient groups. This constitutes 80.7% LTH ICU admissions and 60.5% DGH ICU admissions. The parameters required for this group for use in economic analysis of SDD are ICU-acquired pneumonia and late-onset Gram-negative pneumonia rates, ICU, hospital and six-month mortality; length of ICU stay; total cost; total variable cost; total cost per patient day; and variable cost per patient day. Table 6.10 outlines these parameters. At both centres, ventilated admissions are observed to have a longer ICU stay, higher cost, higher pneumonia rate and higher mortality than the general ICU population. This may be attributable to their ventilation status, or more likely to factors leading them to be ventilated.

Table 6.10 Ventilated Patient Characteristics (First Admission Only)

Patient characteristic	DGH (n=89)	LTH (n=171)
Mean Age (range)	62.6 (18.0-90.8)	59.9 (15.2-89.2)
ICU length of stay[1]	6.44 (4.54-8.34, 0.33-48.73)	7.18 (5.55-8.81, 0.44-66.45)
Hospital length of stay[1]	21.9 (17.1-26.7, 0.4-126.0)	36.2 (29.1-43.3, 1-271)
Episodes of ICU acquired pneumonia per patient[1]	0.22 (0.10-0.34, 0-2.00)	0.64 (0.50-0.78, 0-5.00)
Episodes of Gram negative late onset pneumonia per patient[1]	0.13 (0.06-0.20, 0-2.00)	0.32 (0.23-0.41, 0-3.00)
Total cost per patient/£[1]	6792 (4810-8774, 344-59288)[2]	7715 (5942-9488, 349-82054)[3]
Total variable cost/£[1]	2337 (1921-2753, 117-28145)[4]	3510 (2688-4332, 105-39018)[5]
Total cost per patient day/£[1]	965.8 (924.8-1006.8, 758.4-1728.7)	1122.7 (1067.3-1178.2, 683.5-3021.4)
Variable cost per patient day/£[1]	362.4 (321.4-403.4, 119.3-1092.0)	489.6 (437.5-541.7, 159.8-2327.5)
% ICU mortality	18.0	26.9
% Hospital mortality	38.2	41.6
% 6 month mortality	40.7	50.3

[1] Mean, 95% CI of mean, range; [2] Total cost for this group: £604488

[3] Total cost for this group: £1319214; [4] Total variable cost for this group: £207993

[5] Total variable cost for this group: £600210

6.5 DISCUSSION OF STUDY RESULTS

The primary objective of this study was to obtain a dataset for use in a primary economic analysis. This dataset has four components: patient characteristics, patient costs, infection rates and patient outcomes. This discussion examines to what extent this was achieved by this study, limitations in the methods used and the confidence with which these results can be used in a primary economic analysis.

6.5.1 Overall Study Design

The two centres selected for the study provided epidemiological and economic information for two different ICU environments. The study design was the same for both centres, with a few small methodological changes, discussed below. Patient consent was not a problem at either centre. However, the patient group at DGH was much smaller than anticipated due to a sharp reduction in surgery during the summer of 1994. This may have an impact on the conclusions that can be derived from this smaller dataset.

6.5.2 Patient Characteristics

The patient population was characterised at both study centres. This information was required to identify a hypothetical group at both centres appropriate for SDD therapy. This was carried out by collecting information on the patients' previous and current health status, the primary reason for admission to ICU and other patient-specific information considered relevant. The limitations to the data collected arose mainly

from omissions from the patients' medical histories. APACHE scoring at LTH was done by the same senior clinician through the research period, whereas at DGH, it was carried out by a range of junior and senior clinicians. This may have had an impact on the precision of the scores obtained. When compared with published evidence, the patient populations at the two centres reflect that of British adult mixed (surgical/medical) ICUs. This means that any conclusions drawn from this population are more likely to be generalizable to other district general and large teaching hospitals.

6.5.3 Resource Use and Cost Data

Individual patient costs were derived by recording individual patient resource use and attaching costs to those data. Fixed costs were allocated on a cost per patient day basis. Both centres were able to provide information on ICU and hospital overheads and their allocation methods. There were some differences in the components of the fixed costs at the two centres, but they are still comparable, although the costs supplied by the two centres had to be taken at 'face value'. The fixed cost per patient day was lower at LTH. This is possibly a reflection of a larger ICU with more patients leading to economies of scale. Medical costs were higher at LTH, possibly due to the dedicated nature of medical staffing.

Nursing costs were lower and fluctuated less per patient day through the study period at LTH (Table 6.6). This indicates closer tailoring of nursing requirements to patient occupancy than at DGH. The use of ICS dependency scoring at LTH allowed more accurate allocation of nursing costs to patients on the basis of their nursing dependency. However, this scoring system is relatively crude and subjective, and does not provide

greatly enhanced information. This is illustrated by the fact that nursing costs at LTH tended to behave as fixed costs.

Variable patient costs were obtained by recording all interventions and monitoring undergone by the patient during their ICU stay, and attaching costs to that resource use. Recording of resource use was much more straightforward at LTH as most interventions and monitoring had computerized records. At DGH, written reports inserted into the patient notes had to be relied upon. It was expected that the retrieval of variable resource use would be decreased because of this. Attaching costs to resource use was relatively straightforward at both centres. All clinical support departments were willing to provide current costs for their services, with details of sources and components. As far as could be determined, pathology and radiology departments at both centres used very similar costing methods. Centre-specific information on resource use associated with interventions, such as intubation, was obtained by observation and interview. Most ICU procedures required very similar levels of resources for interventions at the two centres. The acquisition costs of resources used also did not differ greatly because the two centres used the same NHS supplies division. This demonstrates that the difference in variable costs between the two centres was due to differences in treatment intensity, rather than variation in costs.

Both centres had a similar distribution of total patient and variable patient cost. At both centres, the distribution of costs was highly skewed, with some very high cost outliers. This distribution was also observed in the length of stay. At both centres, length of ICU stay correlated strongly with patient costs. The correlation was stronger at LTH. The lower correlation of length of ICU stay with total cost and variable cost at DGH can be attributed to two reasons. The first is that the methods used failed to pick

up all variable costs incurred by the patients, as suggested above. The second is that the ICU is less resource intensive than LTH. If there is less routine monitoring and intervention on a daily basis, then overall variable costs will be lower. Also, rather than carrying out interventions and monitoring on an anticipatory basis, it is suggested that DGH is more reactive in its approach. This would lead to bursts of high resource use consumption rather than a continuous high level. Chapter Seven examines whether the lack of correlation between length of ICU stay and variable cost at DGH is due to this, or to flaws in the data collected. A higher mean variable cost per patient reported at LTH and a very high correlation between length of stay and cost suggests that there is a higher level of routine monitoring and intervention.

Examination of the differences in components of variable costs between the two centres shows that they are increased in most areas at LTH, indicating a higher level of intervention in general. This difference between a district general hospital and a London teaching hospital could be expected. The five principal areas of increased variable cost are blood products, drugs, special beds, radiology and physiotherapy. Increased use of blood products may be attributable to cultural practice differences or the larger proportions of trauma and general surgery carried out at LTH. The increased drug use probably reflects overall increased therapeutic intensity, but may also be affected by the large amounts of sedatives and anaesthetics used in neurosurgical patients. The use of special beds is probably partly cultural, but also due to the high numbers of neurosurgery patients at LTH. The presence of a CT scanner at LTH, combined with the neurosurgical intake, is likely to account for the increased radiology costs. Increased physiotherapy costs may be due to increased levels of treatment or more reliable methods of recording. Reasons for variation in costs are examined statistically in Chapter Seven. The problems associated with

collecting these variable costs at DGH, combined with the smaller patient group, is expected to affect the analysis of factors causing variation in these costs.

6.5.4 Infection Rates

Infection rates were collected at both centres to obtain information on ICU-acquired pneumonia and Gram-negative late-onset pneumonia rates. The rates reported from the two centres are very different. The much higher rate at LTH may be due to many factors. The environment of a large surgical ICU is reported to increase infection rates [George *et al*, 1993]. Also, there may be less stringent infection control procedures at LTH, leading to more cross-infection. An alternative explanation is the increased microbiological monitoring and chest X-rays at LTH leading to more pneumonias being detected or suspected. Pneumonias suspected on the basis of clinical criteria are included in the reported infection rates and associated analysis because pneumonia is difficult to diagnose using microbiological cultures, as discussed in Chapter Three. Therefore, the pneumonia rate at LTH may possibly be artificially high due to over-diagnosis and that at DGH may be artificially low, due to under-diagnosis. The cost attributable to ICU-acquired pneumonia is investigated in Chapter Seven.

At both centres, over half of microbiologically confirmed late-onset pneumonias are Gram-negative. This is the infection rate that would theoretically be reduced by the use of SDD, so is essential for the economic analysis in Chapter Eight. The large difference in this pneumonia rate is expected to significantly affect the overall impact of SDD.

6.5.5 Patient Outcomes

The only patient outcomes recorded by this study are ICU, hospital and six month mortality. No information has been obtained on morbidity or long term mortality, due to time restrictions. As discussed in section 6.3.4, six month mortality is the most useful short term mortality measure. The reasons for the higher mortality at LTH, and whether this can be attributed to the higher ICU-acquired pneumonia rate, is examined in Chapter Seven.

6.5.6 Patients Suitable for SDD Therapy

The final objective of this study was to identify a patient group at both centres that would have been suitable for SDD, if it were implemented at either centre. Published evidence reviewed in Chapter Three suggests ventilated ICU admissions are those most likely to benefit from SDD. Therefore, the ventilated admissions to LTH and DGH were quantified and characterised in terms of defined cost parameters, infection rates and outcomes. A group of only 89 patients was identified at DGH, compared with 171 at LTH. These patient groups are examined in Chapter Seven to assess the impact of pneumonia on resource use and six month mortality. They are then used in Chapter Eight as two groups of patients modelled to receive SDD.

6.6 CONCLUSIONS

The aim of this study was to provide improved economic evidence for the impact of ICU-acquired pneumonia. The cost data obtained are bottom-up, current and practice-based. The sources and components of the costs are explicitly outlined. The discussion above has shown that the resource use and cost collection methods used were as robust as possible. Given the limitations described in the discussion, the costs reported for the patients in this study approximate as closely to their true economic cost (to the intensive care unit) as methodological limitations allow. The stochastic nature of the data means that statistical analysis can be applied to it to identify the resource use attributable to ICU-acquired pneumonia, rather than 'matched pairs' as discussed in Chapter Three. Therefore, it is concluded that these data fulfil the recommendations outlined in Chapter Two.

Chapter 7: Identifying Cost Associated with ICU-Acquired Pneumonia

7.1 INTRODUCTION

Chapter Six has described a prospective study to collect primary economic and epidemiological data on two British ICUs. This chapter describes the analysis of these two datasets to determine the cost and mortality attributable to ICU-acquired pneumonia. The analysis reported in this chapter investigates whether any of the variation in cost observed in this study can be attributed to pneumonia. Variable costs are the cost components that would be expected to vary with pneumonia incidence. Length of ICU stay was shown in Chapter Six to be closely correlated with total variable cost, especially at LTH. Therefore, knowledge of the factors that cause increase in length of ICU stay ultimately provides information on variation in cost. Investigation of variable cost per patient day allows investigation of factors affecting treatment intensity. So, the three cost parameters investigated are total patient variable cost, length of ICU stay and variable cost per patient day. Section 7.2 outlines the specific objectives of the analysis. Section 7.3 provides the theoretical background for the statistical method used. Analysis of the two datasets is reported. The factors affecting the three cost parameters are reported, including the impact of ICU-acquired pneumonia. The subgroups of ventilated admissions at each centre and the impact of ICU-acquired pneumonia on cost in these patients is examined separately. The derivation of increased length of ICU stay and variable cost per patient day attributable to pneumonia is also described. Section 7.4 reports a logit regression analysis to determine whether ICU-acquired pneumonia can explain the difference in

mortality between the two centres. The reasons for selection of the method and its theoretical basis are outlined. The impact of ICU-acquired pneumonia on ventilated admissions is examined. Whether the centre has an independent effect on six month mortality is also examined. Finally, section 7.5 summarises the results of the analyses and discusses their application in the economic analysis of SDD.

7.2 AIMS AND OBJECTIVES OF ANALYSIS

The aim of this analysis is to identify changes in defined cost parameters attributable to ICU-acquired pneumonia both in the general ICU population and in ventilated admissions at DGH and LTH. The specific objectives are to:

1. determine what factors affect total variable cost, length of ICU stay and variable cost per patient day at both centres;

2. determine whether ICU-acquired pneumonia affects these cost parameters, and to what extent, at both centres;

3. derive the increased length of ICU stay and variable cost per patient day attributable to pneumonia;

4. determine what factors affect six month mortality at both centre and

5. determine whether the higher ICU-acquired pneumonia rate at LTH contributes to the higher six month mortality at LTH.

7.3 STATISTICAL ANALYSIS TO IDENTIFY COST DUE TO PNEUMONIA

This section describes the statistical analysis to identify cost due to ICU-acquired pneumonia at the two centres. The theoretical basis of the statistical method selected is outlined. The application of this method to the two datasets is reported. Factors associated with total variable cost, length of ICU stay and variable cost per patient day are elucidated. The extent to which ICU-acquired pneumonia affects these three parameters is investigated. The models derived are then applied to the ventilated patients subgroups. The impact of ICU-acquired pneumonia on the three cost parameters in these patients is elucidated. Finally, the evidence derived from this analysis necessary for economic analysis is summarised.

7.3.1 Selection of Analysis Method

This section discusses the selection of the analysis method. Changes in cost parameters due to ICU-acquired pneumonia are under investigation. Other factors (covariates) influencing cost parameters must be identified and controlled for. Covariates selected are those previously reported in the literature to be significant, including patient admission characteristics and events occurring on ICU. To characterise the association of covariates with one another and with cost parameters, it is necessary to statistically adjust the estimated effects of each covariate for different associations with, and distributions of, the other covariates using *linear multiple regression*. Covariates remaining significant in a multiple regression model are considered independently related to cost, controlling for all other covariates.

7.3.2 Summary of Linear Regression Analysis Method Used

Multiple linear regression allows identification of the impact of one independent variable on a continuous dependent variable, whilst controlling for the effects of other variables (covariates). This produces a linear regression model, containing all significant independent covariates. This section outlines the analysis methods used to derive regression models for the cost parameters listed above.

The cost parameters are expected to be influenced by several independent factors, in the relationship defined in equation 7.1, where y represents the cost parameter.

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_i x_i \qquad [7.1; \text{Sandy, 1990}]$$

In this analysis, ordinary least squares (OLS) linear regression is used to identify the intercept β_0, estimates of the parameters (coefficients) β_1, $\beta_2 \ldots \beta_i$ of independent covariates x_1, $x_2 \ldots x_i$, and the error or variation associated with the estimators. Independent and dependent variables may be transformed to improve relationships, such as log transformation. Log transformation may be appropriate because of the skewed nature of the dependent variable (y). Multicollinearity exists where there is a relationship between independent variables and is often present in observational data. If it exists, the coefficients and explanatory power of the model stay the same, but the variances are increased. This is because there is not enough independent variation in the variable to calculate with confidence the effect it has on the dependent variable [Kennedy, 1993]. This decreases the power of hypothesis testing.

Multicollinearity can be identified using correlation coefficients (ρ). ρ,

however, only identifies two dimensional interaction. Variance inflation factors, VIF_i, are derived from the inverse of the correlation matrix and are given by $(1-R^2_i)^{-1}$. A high VIF indicates an R^2_i near unity and hence suggests collinearity. As a 'rule of thumb', a $VIF_i > 10$ indicates harmful collinearity [Studenmund, 1992]. Multicollinearity can be handled by grouping interacting covariates to form composite variables. An example is 'infection on admission' and 'neurosurgical patient' becoming 'neurosurgical patient infected on admission'.

To assess the goodness of fit of the model, the *sample coefficient of multiple determination, R^2* is used. The 'adjusted' R^2, $\check{R}^2$, adjusts for the number of covariates used in the regression model. $\check{R}^2$ of one indicates a perfect fit. An $\check{R}^2$ of 0.69 is interpreted such that 69% of variation in the data is explained by the model.

The robustness of the model is decreased by the presence of observations that have a disturbing influence on the estimates. Detection of outliers (points unusually far from the regression line or bulk of the data) is necessary to check for measurement error. Outliers are not always influential, so it is also necessary to test for individual observation influence.

An assumption of the OLS procedure is that the error term has a constant variance, that is, it is homoskedastic. Violation of this assumption is common in cross-sectional models. The presence of heteroskedasticity does not change the estimators, just their variance, usually by decreasing it and thus making the model appear more robust than it really is [Studenmund, 1992]. It is necessary to test for heteroskedasticity of the final model. This analysis uses the White test [Studenmund, 1992]. This test derives a test statistic with a Chi-squared (χ^2) distribution. If this

statistic is larger than the critical χ^2 value for the degrees of freedom associated with the model, then the null hypothesis is rejected (χ^2, $p<0.05$) and the conclusion is that the model is heteroskedastic.

7.3.3 Linear Regression Analysis of LTH Dataset

This section outlines the linear regression analysis carried out on the LTH dataset to identify independent predictors of the three cost parameters. Firstly, the covariates listed in Tables 7.1a and 7.1b were investigated individually to assess their unadjusted effect on the three cost parameters. Table 7.1a reports patient admission characteristics that may affect the three cost parameters. Table 7.1b reports recorded events occurring on ICU that may have an impact on the three cost parameters. Three covariates recorded are proxies for organ failure: requirement of dialysis on ICU indicates acute renal failure; requirement of ventilation whilst on ICU indicates acute respiratory failure; requirement of invasive cardiac monitoring by a pulmonary artery catheter (P.A. catheter) indicates acute cardiac failure.

From the initial analysis summarised in Tables 7.1a and 7.1b it can be seen that some covariates exert their effect on total variable cost through the length of ICU stay (such as surgical categories). Some covariates exert their effect on cost per patient day (such as APACHE score). Other covariates have an effect on both length of ICU stay and on treatment intensity, such as dialysis on the ICU. ICU-acquired pneumonia increases total variable cost per patient by increasing length of ICU stay and variable cost per patient day (Table 7.1b). This reported effect is not adjusted by the effects of other covariates. Serious infections acquired on ICU have a marginally significant effect on variable cost.

Many of the covariates[2] significantly affect one another, as shown in Table 7.1b. Many of them are related to the occurrence of pneumonia. For example, the number of days ventilated correlates closely with number of days with a pneumonia ($\rho = 0.794$, $p = 0.0001$). Number of days PA catheterised correlates closely with number of days with a pneumonia ($\rho = 0.606$, $p = 0.0001$). Number of days dialysed correlates with number of days with a pneumonia ($\rho = 0.501$, $p = 0.0001$). This demonstrates the necessity for controlling for these confounding effects by the use of multiple regression techniques, reported in the next three sections.

---

[2]**Covariate Abbreviations and Definitions**

CANCER: Active cancer present at the start of this hospital episode

ELECT: Planned admission to ICU following planned hospital admission/surgery

CPR: Cardiopulmonary resuscitation leading to this ICU admission

CHRONIC: Presence of serious chronic health condition (as defined in APACHE II score)

CARDIAC: Presence of serious chronic cardiac condition (as defined in APACHE II score)

HOSPLOS: Length of hospital stay

IATRO: Unexpected event, other than CPR, occurring immediately prior to ICU admission, such as haemorrhage or fitting.

ICULOS: Length of ICU stay

VENT: Ventilated on admission to ICU

MEDICAL: Has not undergone surgery

NEURO: Has undergone neurosurgery

GENERAL: Has undergone general surgery

TRAUMA: Has undergone multiple surgery for trauma

VASCULAR: Has undergone vascular surgery

OTHER: Has undergone atypical surgery (see section 6.2)

INFECT: Infected on admission to ICU.

Table 7.1a Individual Analysis of Patient Admission Characteristics as Predictors of The Three Cost Parameters (LTH)

Predicting factor	p (Total variable cost)	p (Variable cost per patient day)	p (ICU LOS)
Sex (MALE)	ns	0.0161↑	ns
CANCER	0.0218↓	<0.00005↑	ns
ELECT	0.0004↓	ns	ns
CPR	ns	0.0165↑	ns
IATRO	0.0844↑	0.0055↑	ns
INFECT	0.0004↑	ns	0.0063↑
Age[1]	ns	ns	ns
APACHE II[1]	0.0557↑	0.0010↑[4]	ns
CHRONIC	ns	ns	ns
CARDIAC	<0.00005↑	0.0277↓	<0.00005↑
VENT	0.0098↑	ns	0.0539↑
NEURO[2]	<0.00005↓	0.0016↓	<0.00005↓
GENERAL[2]	ns	0.0957↑	ns
VASCULAR[2]	0.0037↓	0.0101↑	0.0357↓
TRAUMA[2]	0.0001↑	ns	0.0094↑
OTHER[2]	ns	0.0297↓	0.0695

[1] Correlation test. All other significance tests: t-test

[2] Significance compared with 'medical' category

[3] $\rho = 0.278$ (significant, $p < 0.01$)

[4] $\rho = 0.227$ (significant, $p < 0.01$)

↑ Cost parameter increases in presence of risk factor

↓ Cost parameter decreases in presence of risk factor

Table 7.1b Individual Analysis of Relationship of Events on ICU with The Three Cost Parameters (LTH)

Predicting factor	p (Total variable cost)	p (Variable cost per patient day)	p (ICULOS)
Ventilated during ICU stay	0.008↑	0.013↑	0.0095↑[1]
Dialysed during ICU stay	0.0001↑	0.0001↑	0.0001↑[2]
PA catheter during ICU stay	0.0001↑	0.0002↑	0.0001↑[3]
Serious infection during ICU stay	0.1069↑	ns	ns
Pneumonia during ICU stay	0.0060↑	<0.00005↑	0.0081↑[4]
ICU survival	0.0014↓	<0.00005↓	ns

[1]Number of days ventilated correlated closely with ICU length of stay ($\rho = 0.934$, $p = 0.0001$).

[2]Number of days dialysed correlated closely with ICU length of stay ($\rho = 0.701$, $p = 0.0001$)

[3]Number of days with a pulmonary catheter in situ correlated closely with ICU length of stay ($\rho = 0.788$, $p = 0.0001$)

[4]Number of days with a pneumonia correlated closely with ICU length of stay ($\rho = 0.899$, $p = 0.0001$)

↑ Cost parameter increases in presence of risk factor

↓ Cost parameter decreases in presence of risk factor

7.3.3.1 Linear Regression Analysis of Total Variable Cost per Patient at LTH

This section reports the linear regression analysis of factors affecting total variable cost per patient at LTH. OLS regression was used to develop a linear regression model, using the methods described in section 7.3.2.

Initially, a correlation matrix was derived for all the covariates in the analysis. This detected the extent of two-dimensional interaction between the covariates. Marginally significant multicollinearity (n = 212, critical $\rho = 0.164$, p = 0.05) was detected between many combinations of covariates. Interacting combinations of covariates that produced independently significant combinations were OTHER (surgery) and IATRO(genic event), and ICU mortality and APACHE. The first combination indicates that iatrogenic events, other than CPR, occurring in surgery only have a significant effect on total variable cost when the patient has undergone atypical surgery. The second combination suggests that severity of illness is only associated with an increase in total variable cost in patients who do not survive ICU. All the variance inflation factors (VIFs) in the final model were less than 1.5. Heteroskedasticity was not a problem in the untransformed model (White test; p = 0.1412 [Studenmund 1992]). The intercept and coefficients of independently significant covariates are reported in the model derived in Table 7.2.

Table 7.2 Regression Model for Explaining Total Variable Cost per Patient at LTH

Source	Estimate (β_n)	Standard error of β_n	T for H_0[1]	P > |T|
Intercept (β_0)	-652.2	228.0	-2.861	0.0047
CHRONIC	-415.06	210.7	-1.965	0.0551
APACHE ICU mortality composite [2]	68.2	12.0	5.695	0.0001
OTHER/IATRO composite [3]	409.2	198.0	2.066	0.0401
ICU length of stay	475.6	10.6	45.002	0.0001
VASCULAR surgery	1079.7	303.2	3.562	0.0005
GENERAL surgery	792.3	276.7	2.864	0.0046
TRAUMA surgery	1406.4	527.1	2.668	0.0083

[1] Null Hypothesis: Parameter = 0

[2] Composite = APACHE x ICU mortality

[3] Composite = Other surgery x iatrogenic event

The $\check{R}^2$ of the model was 0.911 ($F = 301.18$, $p = 0.0001$), indicating that the model explains 91.1% of the variation in total variable cost per patient. Twelve outliers were identified but when tested for influence, were not found to cause significant disturbance in the model. Most explanatory power comes from ICU length of stay ($\rho = 0.948$). This model suggests that the presence of chronic illness decreases the total variable cost of the patient. Admissions from vascular, general and trauma surgery increase variable cost significantly over medical patients. Neurosurgery patients do

not have a significantly larger total variable cost than medical patients, once the other factors in the model are taken into account, so are lost from the model. If the patient is dialysed on ICU, there is a significant impact on total variable cost. However, there was significant correlation between dialysis occurring on ICU with length of ICU stay ($\rho = 0.41$). This interaction significantly increases the error estimates of coefficients for both covariates. This implies that dialysis on ICU increases length of ICU stay and increases the intensity of treatment whilst on ICU, as demonstrated in the individual analysis. Because of this joint effect, this factor cannot be included in a model that contains length of stay, due to the interaction. Removing the dialysis covariate did not greatly affect explanatory power. However, the interaction suggests that examination of length of ICU stay separately from treatment intensity is necessary to control for factors that impact on both components of total variable cost. Moreover, ICU-acquired pneumonia and insertion of a PA catheter are not shown to have a significant effect on total variable cost. However, they have both been shown to individually affect ICU length of stay. This analysis demonstrates, therefore, that it is necessary to examine the two components of total variable cost separately, that is, build regression models for ICU length of stay and variable cost per patient day separately. Isolation of the effect of dialysis, pneumonia and PA catheters on length of ICU stay and treatment intensity, as well as the other covariates, is examined in the next two models.

If ICU-acquired pneumonia is included in the model derived above, it has a marginally significant impact on total variable cost ($\beta = £432.4$, 95% CI = £0 - £924.36, $p = 0.0869$). $\check{R}^2$ is not affected but the model becomes heteroskedastic (White test; $p = 0.0365$). In the individual analysis it is suggested that pneumonia exerts its effect on length of ICU stay. Therefore the presence of ICU stay in the model effectively controls for the

effect of pneumonia, explaining the non-significance of ICU-acquired pneumonia in this model. It is possible that a larger dataset would have demonstrated a significant effect. ICU-acquired serious infections other than pneumonia were not shown to have a significant effect.

7.3.3.2 Linear Regression Analysis of ICU Length of Stay at LTH

OLS regression was used to develop a linear regression model to explain variations in length of ICU stay. On examination of interaction, the only interacting combination of covariates that produced independently significant composites was ICU mortality and APACHE. This combination implies that, in patients who die on the ICU, the more severely ill they are, the shorter their length of ICU stay. All the variance inflation factors (VIFs) in the final model were less than 1.5. Heteroskedasticity was a problem in the untransformed model (White test; $p<0.0001$ [Studenmund 1992]). Log transformation of length of ICU stay was required to render the data homoskedastic (White test: $p=0.136$). The semi-log (log-lin) model derived is outlined in Table 7.3.

Table 7.3 Regression Model for Explaining Log ICU Length of Stay at LTH

Source	Estimate (β_n)	Standard error of β_n	T for H_0[1]	P> |T|
Intercept (β_0)	0.484	0.082	5.894	0.0001
APACHE ICU mortality composite[2]	-0.001	0.0002	-5.216	0.0001
Dialysed during stay	0.836	0.202	4.133	0.0001
PA[3] catheter during stay	0.441	0.146	3.023	0.0028
ICU-acquired pneumonia	1.131	0.127	10.323	0.0001

[1] Null hypothesis: Parameter = 0

[2] Composite = APACHE[2] x ICU mortality (this composite was required to produce the highest $\check{R}^2$, to ensure that the intercept was significant and to reduce interaction).

[3] PA catheter: pulmonary artery catheter inserted during ICU stay

$\check{R}^2$ of the model was 0.510 (F = 54.65, p = 0.0001), indicating that the model explains 51.0% of the variation in log length of ICU stay. Unexplained variation may be explained by insufficient data, omission of explanatory covariates or complex relationships between length of stay and covariates not detected by this analysis. The model is interpreted such that the coefficients represent the percentage increase in the length of stay. Therefore, being dialysed whilst on ICU increases the length of stay by 83.6% (95% CI: 44.1%-123.4%) and the insertion of a PA catheter is associated with a 44.1% (95% CI: 15.5%-72.7%) increase in length of ICU stay. Ten outliers were identified but when tested for influence, were not found to cause significant disturbance in the semi-log model.

Being *admitted* with pneumonia was not shown to affect ICU length of stay. Acquiring a pneumonia whilst on ICU is associated with an increased length of ICU stay. In the regression model, an episode of ICU acquired pneumonia increases length of ICU stay by 113% (95% CI: 88.2%-138.0%). Serious infections other than pneumonia did not retain an independent effect on length of ICU stay.

7.3.3.3 Linear Regression Analysis of Variable Cost per Patient Day at LTH

OLS regression was used to develop a linear regression model to explain variations in variable cost per patient day. On examination of interaction, interacting combinations of covariates that produced independently significant composites were NEURO and INFECT, OTHER and IATRO, VASCULAR and AGE, ICU mortality and APACHE. These combinations can be interpreted such that neurosurgical patients admitted with infections; atypical surgery patients admitted after iatrogenic events in surgery; older vascular surgery patients and severely ill patients who subsequently die incur the greater treatment intensity. Whether the patient was dialysed or had a pulmonary artery catheter were also significantly correlated with one another ($\rho = 0.450$). All the variance inflation factors (VIFs) in the final model were less than 2. Heteroskedasticity was not a problem in the untransformed model (White test; $p = 0.7809$ [Studenmund 1992]). The model derived is outlined in Table 7.4.

Table 7.4 Regression Model for Explaining Variable Cost per Patient Day at LTH

Source	Estimate (β_n)	Standard error of β_n	T for H_0[1]	P > |T|
Intercept (β_0)	368.9	39.0	9.450	0.0001
CHRONIC	-100.8	42.1	-2.394	0.0176
APACHE ICU mortality composite[2]	0.4	0.1	3.981	0.0001
OTHER/IATRO composite[3]	89.3	36.0	2.483	0.0139
Infected neurosurgery patient [4]	1059.0	288.3	3.674	0.0003
VASCULAR/AGE composite[5]	2.0	0.7	2.616	0.0096
GENERAL surgery	215.4	50.1	4.297	0.0001
Dialysed or PA catheter during ICU[6]	403.6	138.3	2.919	0.0039
ICU-acquired pneumonia	51.0	24.1	2.119	0.0354

[1] Null Hypothesis: Parameter = 0

[2] Composite = $(\text{APACHE})^2$ x ICU mortality

[3] Composite = Other surgery x iatrogenic event

[4] Composite = Neurosurgery x infected on admission

[5] Composite = Vascular surgery x age

[6] Composite = Proportion of ICU stay dialysed or pulmonary artery catheter present

The $\check{R}^2$ of the model was only 0.295 ($F = 11.78$, $p = 0.0001$), indicating that the model only explains 29.5% of the variation in variable cost per patient day, or treatment intensity. This can be explained by insufficient data, omission of explanatory covariates or complex relationships not

detected by this analysis. Seven outliers were identified but when tested for influence, were not found to cause significant disturbance in the model.

Being admitted with pneumonia was not shown to affect cost per patient day. ICU-acquired pneumonia increases variable cost per patient day by £51.0 (95% CI: £4.1-£98.2). Other serious infections were not shown to have a significant effect.

7.3.3.4 Summary of Linear Regression Analysis of Cost Parameters at LTH

In summary, this analysis demonstrates that, in all eligible first admissions to LTH ICU, an episode of ICU-acquired pneumonia has an independent effect on:

1. length of ICU stay, increasing it by 113% (95% CI: 88% - 138%);
2. treatment intensity, increasing variable cost per patient/day by £51.0 (95% CI: £4.1 - £98.2) (10.2% increase from mean).

7.3.3.5 Linear Regression Analysis of Factors Affecting Cost Parameters in Ventilated Patients at LTH ICU

The models described above were run on ventilated admissions only (n = 171). The $\check{R}^2$ of the models were not at all significantly different. ICU-acquired pneumonia increased ICU length of stay by 116% (95% CI: 88.0% - 144.0%, p = 0.0001). Variable cost per patient day was increased by £53.3 (95% CI: 2.4 - 101.3, p = 0.049). Total variable cost per patient was marginally significantly increased by £473.6 (95% CI: 0 - £1048.5, p = 0.10).

7.3.4 Derivation of Changes In Cost Parameters Attributable to ICU-Acquired Pneumonia at LTH

For economic analysis, the actual changes in resource use due to an episode of ICU-acquired pneumonia in a ventilated patient are required. From the regression analysis reported above, it is known that length of ICU stay is increased by 116% and variable cost per patient day is increased by £53.3. However, it is not known from what value the increase occurs. Therefore, the actual length of ICU stay and variable cost per patient day for ventilated patients who do and do not experience an episode of ICU-acquired pneumonia is not known. This section describes how these values can be derived from the information already known.

It is known that the mean ICU length of stay of ventilated patients is 7.18 days, the mean variable cost per patient day is £489.6, the incidence of ICU-acquired pneumonia is 0.64 episodes per ventilated patient (see Table 6.10) and an episode increases ICU length of stay by 116% and variable cost per patient day by £53.3. From this it is possible to derive lengths of stay and variable costs per patient day for infected and uninfected patients[3]. These derived values represent the lengths of ICU stay and variable costs per patient day for two theoretical groups of ICU patients. The lengths of ICU stay and variable cost per patient day of these two groups have been controlled for the effects of the other factors shown to be significant by the regression analysis. Therefore, the only difference

---

[3] 0.36(uninfected LOS) + 0.64(infected LOS) = 7.18, where
infected LOS = 2.16 x uninfected LOS

0.36(uninfected variable cost per patient/day) + 0.64(infected variable cost per patient/day) = £489.6, where infected cost = uninfected cost + £53.3

between these two groups (within the limits of this regression analysis) is that one group does and one group does not experience an episode of ICU-acquired pneumonia. The derived difference represents the difference independently attributable to that episode of pneumonia. The derived differences are reported in Table 7.5a.

Table 7.5a also reports total costs. As the length of ICU stay is known, it was possible to calculate the fixed costs that are associated with that length of stay. The total cost per patient with and without an episode of ICU-acquired pneumonia is the cost parameter required for economic evaluation of SDD.

Table 7.5a Changes in Resource Use Associated with ICU-Acquired Pneumonia in Ventilated Patients at LTH

Resource Use Parameter	Cost/£
Length of stay of uninfected patient/days[1]	4.1
Length of stay of patient with ICU-acquired pneumonia/days[1]	8.9
Variable cost per patient day for uninfected patients/£[1]	456.0
Variable cost per patient day for infected patients[1]	508.8
Total variable cost per uninfected patient/£[2]	1869.6
Total cost per uninfected patient/£[3]	4198.8
Total variable cost per patient with ICU-acquired pneumonia/£[4]	4528.3
Total cost per patient with ICU-acquired pneumonia/£[3]	9584.4
Increase in total cost due to ICU-acquired pneumonia/£	5385.6

[1] Derived values

[2] Value derived from derived ICU length of stay and variable cost per patient day for uninfected ventilated patients

[3] Fixed costs (£129.1), nursing costs (mean £307.0) and medical staff costs (£132) added back to variable cost to give total cost per ventilated patient

[4] Value derived from derived ICU length of stay and variable cost per patient day for infected ventilated patients

The derived total cost for uninfected and infected ventilated patients is £4199 and £9584. Confidence intervals cannot be quoted because the variable cost per patient day used for infected and uninfected patients is a derived value. These derived costs per patient are used in the primary economic analysis in Chapter Eight. The ranges of the parameters for sensitivity analysis in Chapter Eight are listed in Table 7.5b.

Table 7.5b Ranges of Parameters Required for Economic Analysis for the LTH Dataset

Parameter for Use in Economic Analysis	Ranges for Sensitivity Analysis
Increase in length of ICU stay due to pneumonia derived from linear regression	88%-144%
Length of stay of uninfected patient/days[1]	3.7, 4.6
Length of stay of patient with ICU-acquired pneumonia/days[1]	8.7, 9.2
Increase in variable cost per patient/day due to pneumonia derived from linear regression/£	2.4-101.3
Variable cost per patient/day for uninfected patients/£[2]	424.8, 488.1
Variable cost per patient/day for infected patients[2]	490.5, 526.1

[1] Uninfected and infected lengths of stay derived from 88% increase in length of ICU stay are 4.6 and 8.7 days respectively. Uninfected and infected lengths of stay derived from 144% increase in length of ICU stay are 3.7 and 9.2 days respectively.

[2] Uninfected and infected variable cost derived from £2.4 increase are £488.1 and £490.5 respectively. Uninfected and infected variable cost derived from £101.3 increase are £424.8 and £526.1 respectively.

7.3.5 Linear Regression Analysis of DGH Dataset

This section outlines the linear regression analysis carried out on the DGH dataset to identify independent predictors of the three cost parameters. Firstly, the covariates listed in Tables 7.6a and 7.6b were investigated individually to assess their unadjusted effect on the three cost parameters. Table 7.6a reports patient admission characteristics that may affect the three cost parameters. Table 7.6b reports recorded events occurring on ICU that may have an impact on the three cost parameters. Three

covariates recorded are proxies for organ failure (see section 7.3.3).

From this initial analysis summarised in Tables 7.6a and 7.6b it can be seen that, as with the LTH dataset, covariates exert their effect on total variable cost through the length of ICU stay or through cost per patient day. Other covariates have an effect on both length of ICU stay and on treatment intensity. ICU-acquired pneumonia increases total variable cost per patient by increasing length of ICU stay. There is no detectable increase in variable cost per patient day (Table 7.6b). These effects are not adjusted for the effects of other covariates. Serious infections acquired on ICU have a significant effect on variable cost through their effect on length of stay. As 78.6% of ICU-acquired serious infections at DGH are pneumonias, it is likely that this reflects the effect of ICU-acquired pneumonias.

Many of the covariates significantly affect one another, as illustrated in Table 7.6b. Many of them are related to the occurrence of pneumonia. For example, the number of days ventilated correlated closely with number of days with a pneumonia ($\rho = 0.858$, $p = 0.0001$). Number of days PA catheterised correlated closely with number of days with a pneumonia ($\rho = 0.473$, $p = 0.0001$). Number of days dialysed correlated with number of days with a pneumonia ($\rho = 0.535$, $p = 0.0001$). This again demonstrates the necessity for controlling for these confounding effects by the use of multiple regression techniques, reported in the next three sections.

Table 7.6a Analysis of Patient Characteristics as Predictors of The Three Cost Parameters (DGH)

Predicting factor	p (Total variable cost)	p (Variable cost per patient day	p (ICU LOS)
Sex (MALE)	0.0107↑	ns	<0.00005↑
CANCER	ns	ns	ns
ELECT	<0.00005↓	ns	0.0324↓
CPR	0.0272↑	ns	ns
IATRO	0.0380↑	ns	ns
INFECT	<0.00005↑	0.0202↑	0.0018↑
Age[1]	ns	ns	ns
APACHE II[1]	0.0105[3]	ns	0.009[4]
CHRONIC	<0.00005↑	ns	ns
CARDIAC	<0.0003↓	ns	<0.003↓
VENTILATED	<0.00005↑	ns	<0.00005↑
READMISSION	ns	<0.00005↑	0.0333↑
GENERAL[2]	0.0048↑	ns	0.0007↑
VASCULAR[2]	0.0036↓	ns	ns
TRAUMA[2]	0.0037↓	ns	0.0026↓
OTHER[2]	0.0566↓	0.085↓	0.0001↓
ICU survivor	ns	ns	0.0090↓

[1] Correlation test. All other significance tests: t-test.

[2] Significance compared with 'medical' category

[3] $\rho = 0.223$ ($p < 0.01$)

[4] $\rho = 0.228$ ($p < 0.01$)

↑ Cost parameter increases in presence of risk factor

↓ Cost parameter decreases in presence of risk factor

Table 7.6b Individual Analysis of Relationship of Events on ICU with the Three Cost Parameters (DGH)

Predicting factor	p (Total variable cost)	p (Variable cost per patient day)	p (ICULOS)
Ventilated during ICU stay	<0.00005↑	0.0832↑	<0.00005↑[1]
Dialysed during ICU stay	<0.00005↑	0.018↑	<0.00005↑[2]
PA catheter during ICU stay	<0.00005↑	ns	<0.00005↑[3]
Serious infection during ICU stay	0.045↑	ns	<0.00005↑
Pneumonia during ICU stay	<0.00005↑	ns	<0.00005↑[4]
ICU survival	ns	ns	0.0090↓

[1]Number of days ventilated correlated closely with ICU length of stay ($\rho = 0.667$, $p = 0.0001$).

[2]Number of days dialysed correlated with ICU length of stay ($\rho = 0.538$, $p = 0.0001$)

[3]Number of days with a pulmonary catheter in situ correlated with ICU length of stay ($\rho = 0.490$, $p = 0.0001$)

[4]Number of days with a pneumonia correlated closely with ICU length of stay ($\rho = 0.630$, $p = 0.0001$)

↑ Cost parameter increases in presence of risk factor

↓ Cost parameter decreases in presence of risk factor

7.3.5.1 Linear Regression Analysis of Total Variable Cost per Patient at DGH

This section reports the linear regression analysis of factors affecting variable cost per patient at DGH. OLS regression was used to develop a linear regression model, using the methods described in section 7.3.2. No interacting combinations of covariates produced independently significant

principal components. The $\check{R}^2$ of the model was improved if the cube product of ICU length of stay was used. The model derived is outlined in Table 7.7.

Table 7.7 Regression Model for Predicting Total Variable Cost per Patient at DGH

Source	Estimate (β_n)	Standard error of β_n	T for H_0[1]	$P > \|T\|$
Intercept (β_0)	1545.5	865.4	1.786	0.0766
APACHE	85.7	29.1	2.950	0.0038
Age	-30.5	13.5	-2.254	0.0260
(ICU length of stay)^3	0.17	0.02	8.280	0.0001
VENT	926.4	444.2	2.086	0.0391
Dialysed whilst on ICU	2005.6	876.9	2.287	0.0239

[1] Null Hypothesis: Parameter = 0

The model produced had no VIF values over 1.5, so harmful multicollinearity was not present. The $\check{R}^2$ was 0.531 ($F = 25.32$, $p = 0.0001$), indicating that the model explains 53.1% of the variation in total variable cost per patient. However, this model is significantly heteroskedastic (White test: $p < 0.0005$). Obtaining a homoskedastic model required the use of fewer covariates to produce the model outlined in Table 7.8.

Table 7.8 Revised Regression Model for Explaining Total Variable Cost per Patient at DGH

Source	Estimate (β_n)	Standard error of β_n	T for H_0[1]	P > |T|
Intercept (β_0)	1147.5	216.6	5.297	0.0001
(ICU length of stay)^3	0.16	0.02	8.119	0.0001
Dialysed whilst on ICU	2288.3	911.4	2.511	0.0132

[1] Null Hypothesis: Parameter = 0

The model produced had no VIF values over 1.5, so harmful multicollinearity was not present. The $\check{R}^2$ was 0.464 ($F = 59.81$, $p = 0.0001$), indicating that the model explains 46.4% of the variation in total variable cost per patient. The model has a homoskedastic error distribution (White test; $p = 0.611$). Chapter Six discussed the possible reasons for the lack of correlation between length of ICU stay and total variable cost per patient at DGH. The possible reactive nature of therapeutic intervention at DGH leading to a different distribution in variable cost is not supported by this linear regression analysis. Whilst therapeutic interventions affect variable cost on an individual basis (see Table 7.6b), none apart from dialysis retain independent significance in the regression model. This suggests that there may be flaws in the collection of resource use data relating to variable cost.

When ICU-acquired pneumonia was added to the regression model, it tended towards significance but did not reach it ($p = 0.15$).

7.3.5.2 Linear Regression Analysis of ICU Length of Stay at DGH

OLS regression was used to develop a linear regression model to explain variations in length of ICU stay. Marginally significant multicollinearity (n = 137, critical $\rho = 0.220$, p = 0.05) was detected between many combinations of covariates, such as AGE and APACHE. ICU mortality and APACHE score were the only interacting covariates to produce independently significant composites. As at LTH, patients that die on ICU have a shorter length of ICU stay the more severely ill they are. Obtaining a homoskedastic model required log transformation of length of stay to produce the semi-log (log-lin) model outlined in Table 7.9.

Table 7.9 Regression Model for Explaining Log ICU Length of Stay at DGH

Source	Estimate (β_n)	Standard error of β_n	T for H_0[1]	P > |T|
Intercept (β_0)	-0.562	0.231	-2.435	0.0163
APACHE	0.039	0.011	3.573	0.0005
ICU mortality	-0.589	0.234	-2.516	0.0131
Male patient	0.592	0.165	3.589	0.0005
Ventilated on admission	0.387	0.167	2.325	0.0217
ICU-acquired pneumonia	1.090	0.146	7.485	0.0001

[1] Null hypothesis: Parameter = 0

The semi-log model produced had no VIF values over 1.5, so harmful

multicollinearity was not present. The $\check{R}^2$ was 0.456 ($F = 22.58$, $p = 0.0001$), indicating that the model explains 45.6% of the variation in log length of ICU stay. The model is interpreted such that the estimates of the coefficients represent the percentage increase in the length of stay. Therefore, being ventilated on admission to ICU increases the length of stay by 38.7%. Six outliers were identified but did not cause significant disturbance in the model.

Being *admitted* with pneumonia was not shown to affect ICU length of stay. ICU-acquired pneumonia increases length of ICU stay by 109% (95% CI: 80.4% - 137.6%). Neither pneumonia covariates significantly interacted with other covariates. ICU-acquired serious infections had no significant effect once ICU-acquired pneumonia was controlled for.

7.3.5.2 Linear Regression Analysis on Variable Cost per Patient Day at DGH

OLS regression was used to develop a linear regression model to explain variations in variable cost per patient day. No interacting combinations of covariates produced significant composites. The regression model derived is outlined in Table 7.10.

Table 7.10 Regression Model for Explaining Variable Cost per Patient Day at DGH

Source	Estimate (β_n)	Standard error of β_n	T for H_0[1]	P > |T|
Intercept (β_0)	264.2	21.1	12.603	0.0001
IATRO	143.1	48.4	2.958	0.0037
PA catheter whilst on ICU	68.2	36.3	1.881	0.0622

[1] Null Hypothesis: Parameter = 0

The regression model reported in Table 7.10 was the only model that had a significant intercept, had a homoskedastic error distribution (White test; p = 0.1095) and individually significant covariate estimators. The model produced had no VIF values over 1.5, so harmful multicollinearity was not present. The $\check{R}^2$ was only 0.070 (F = 6.19, p = 0.0027), indicating that the model only explains 7.0% of the variation in log variable cost per patient day, or treatment intensity. This may be explained by insufficient data, omission of explanatory covariates or complex relationships not detected by this analysis. It is likely that this lack of explanatory power is due to flaws in the collection of resource use data relating to variable cost.

Being *admitted* with pneumonia was not shown to affect cost per patient day. ICU-acquired pneumonia did not independently affect variable cost per patient day. Other ICU-acquired serious infections were also not shown to have a significant effect.

7.3.5.3 Summary of Linear Regression Analysis of Cost Parameters at DGH

In summary, this analysis demonstrates that, in all eligible first admissions to DGH ICU, an episode of ICU-acquired pneumonia has:

1. an independent effect on length of ICU stay at DGH, increasing it by 109%;
2. no independent effect on treatment intensity, showing no increase in variable cost per patient day;
3. no independent effect on total variable cost over and above that due to increase in length of ICU stay.

7.3.5.4 Linear Regression Analysis of Factors Affecting Cost Parameters in Ventilated Patients at DGH ICU

The models described above were run on ventilated admissions only (n=89). The $\check{R}^2$ of the models were not significantly different from the models derived from the entire ICU population. ICU-acquired pneumonia increased ICU length of stay in ventilated admissions by 111% (95% CI: 78.3% - 143.7%, p=0.0001). Total variable cost and variable cost per patient/day were not affected by ICU-acquired pneumonia.

7.3.6 Derivation of Resource Use Changes Attributable to ICU-Acquired Pneumonia at DGH

For economic analysis, the actual changes in resource use due to an episode of ICU-acquired pneumonia are required. From the regression

analysis above, it is known that the mean ICU length of stay of ventilated patients is 6.44 days, the incidence of ICU-acquired pneumonia is 0.22 episodes per ventilated patient and an episode increases ICU length of stay by 111%. However, as with the LTH dataset, it is not known from what value the increase occurs. Again, the actual length of ICU stay and variable cost per patient day for ventilated patients who do and do not experience an episode of ICU-acquired pneumonia is not known. In this section, these values are derived from the information already known, using the same methods as reported in section 7.3.4.

It is known that the mean ICU length of stay of ventilated patients is 6.44 days, the incidence of ICU-acquired pneumonia is 0.22 episodes per ventilated patient (Table 7.10) and an episode increases ICU length of stay by 111%. With this information, it is possible to derive hypothetical lengths of stay for infected and uninfected patients[4]. As for the LTH dataset, these values represent the lengths of ICU stay for two theoretical groups of ICU patients. The lengths of ICU stay and variable cost per patient/day of these two groups have been controlled for the effects of the factors shown to be significant by the regression analysis. Therefore, the only difference between these two groups (within the limits of this regression analysis) is that one group does and one group does not experience an episode of ICU-acquired pneumonia. The derived difference represents the difference independently attributable to that episode of pneumonia. The derived differences are reported in Table 7.11a.

Table 7.11a also reports total costs. As the length of ICU stay is known, it was possible to calculate the fixed costs that are associated with that

---

[4] 0.78(uninfected LOS) + 0.22(infected LOS) = 6.44, where infected LOS = 2.11 x uninfected LOS

length of stay. The total cost per patient with and without an episode of ICU-acquired pneumonia is the cost parameter required for economic evaluation of SDD.

The derived costs for uninfected and infected ventilated patients are reported in Table 7.11a to be £5207 and £10915 respectively. Confidence intervals are quoted in the table because the variable cost per patient day is the actual value obtained from the data, not a derived value as at LTH. The values derived here are used in the primary economic analysis in Chapter Eight. In the sensitivity analysis, all the parameters are varied to assess the impact of their variation. The ranges of the parameters are listed in Table 7.11b. The ranges of variable costs per day are combined with the ranges of lengths of ICU stay, and their associated fixed costs, to provide a range of costs for sensitivity analysis.

Table 7.11a Changes in Resource Use Associated with ICU-Acquired Pneumonia in Ventilated Patients at DGH

Resource Use Parameter	Value
Length of stay of uninfected patient/days[1]	5.2
Length of stay of patient with ICU-acquired pneumonia/days[1]	10.9
Variable cost per patient day[2] for infected and uninfected patients (95% CI)	362.4 (4.8-720.0)
Total variable cost per uninfected patient/£[3] (95% CI)	1884 (24-3744)
Total cost per uninfected patient/£ (95% CI)[4]	5207 (3347-7067)
Total variable cost per patient with ICU-acquired pneumonia/£[5] (95% CI)	3950 (52-7848)
Total cost per patient with ICU-acquired pneumonia/£ (95% CI)[4]	10915 (7017-14813)
Increase in variable cost due to ICU-acquired pneumonia/£	5708

[1] Derived values

[2] Mean, 95% CI

[3] Value derived from derived ICU length of stay for uninfected ventilated patient, mean variable cost per patient day for ventilated admissions. Upper and lower ranges derived from 95% CI of variable cost per patient day.

[4] Fixed costs (£182.6), nursing costs (mean £332.4) and medical staff costs (£124) added back to variable cost to give total cost per patient

[5] Value derived from derived ICU length of stay for infected ventilated patient and mean variable cost per patient day for ventilated admissions. Upper and lower ranges derived from 95% CI of variable cost per patient day.

Table 7.11b Ranges of Parameters Required for Economic Analysis for the DGH Dataset

Parameter for Use in Economic Analysis	Ranges for Sensitivity Analysis
Increase in length of ICU stay due to pneumonia derived from linear regression	78-144%
Length of stay of uninfected patient/days[1]	4.9, 5.5
Length of stay of patient with ICU-acquired pneumonia/days[1]	9.8, 11.9
Increase in variable cost per patient day due to pneumonia derived from linear regression/£	0
Variable cost per patient day for uninfected and infected patients/£[2] (95% CI of mean)	362.4 (119.3-1089.6)

[1] Uninfected and infected lengths of stay derived from 78% increase in length of ICU stay are 5.5 and 9.8 days respectively. Uninfected and infected lengths of stay derived from 144% increase in length of ICU stay are 4.9 and 11.9 days respectively.

[2] Uninfected and infected variable costs are the same, so the mean variable cost per patient day is used. The ranges used for sensitivity analysis are 95% confidence intervals of the mean.

7.4 STATISTICAL ANALYSIS TO IDENTIFY MORTALITY DUE TO PNEUMONIA

The six month mortality rates at LTH and DGH are 50.3% and 40.7%, respectively. The ICU-acquired pneumonia rates at LTH and DGH are 65% and 28%, respectively. This section describes the statistical analysis to examine whether the higher ICU-acquired pneumonia rate at LTH explains the higher six month mortality at LTH. This is done by identifying whether mortality can be attributed to ICU-acquired pneumonia at the two centres. From published evidence, it is not expected to detect a difference in

mortality due to ICU-acquired pneumonia (see Chapter Three, section 3.4.2), unless there is a large attributable mortality. This is due to a small patient population and the presence of many confounding factors. Factors contributing to the difference in mortality between the two centres is examined. Firstly, the selection of the most appropriate method for identification of mortality attributable to ICU-acquired pneumonia is discussed. Six month mortality is the most 'useful' short term mortality parameter, so is the parameter investigated in this analysis. The theoretical basis of the statistical method selected is outlined. The application of this analysis technique to the two datasets is reported. Factors associated with mortality are elucidated. The extent to which ICU-acquired pneumonia affects mortality is investigated. The models derived are applied to the ventilated patients subgroups. This allows assessment of the impact of ICU-acquired pneumonia on mortality in these patients.

7.4.1 Selection of Research Method

The aim of this analysis is to identify and quantify the effect of ICU-acquired pneumonia on patient six-month mortality, in all eligible ICU admissions and ventilated eligible ICU admissions. Identification and quantification of the effect of ICU-acquired pneumonia on mortality requires that other factors influencing mortality must be identified and controlled for. Eligible first admissions to each ICU were analysed to assess which factors affected six month outcome. Covariates selected were those previously reported in the literature to be significant. To characterise the association of covariates with one another and with mortality, it is necessary to statistically adjust the estimated effects of each covariate for different associations with, and distributions of, the other covariates [Hosmer *et al*, 1989]. The technique used when the dependent variable is

dichotomous is *logit regression*. The theoretical basis of this technique is outlined in the next section. Logit regression is used to identify independent predictors of six month mortality, to assess the impact of ICU-acquired pneumonia.

7.4.2 Summary of Logit Regression Analysis Method Used

The goal of logit regression is to find the best-fitting model, with *a priori* logic, to describe the relationship between a dichotomous dependent variable and a set of independent variables (covariates) [Hosmer *et al*, 1989]. Logit regression follows the same general principles as linear regression, differing primarily in the choice of the parametric model and assumptions. The model uses the logistic distribution, where the curve is 'S'-shaped. The specific form of this model is:

$$\pi(x) = \frac{e^{\beta 0 + \beta 1 x}}{1 + e^{\beta 0 + \beta 1 x}} \qquad (7.2)$$ [Hosmer *et al*, 1989]

where (x) represents the conditional mean of the dependent variable (Y) given x. The logit transformation of this expression gives the following:

$$g(x) = \ln \frac{\pi(x)}{1-\pi(x)} \qquad (7.3)$$

$$= \beta_0 + \beta_1 x \qquad (7.4)$$

Equation 7.4 gives the expression central to logit regression modelling, for a logit model with one independent variable.

Where there is more than one independent variable, the expression becomes:

$$g(x) = \beta_0 + \beta_1 a + \beta_2 b \ldots . \beta_n j \qquad (7.5)$$

where (x) represents the conditional mean of Y given a, b....j.

7.4.2.1 Fitting the Logit Regression Model

To fit the logit regression model in equation 7.5 to a set of data requires estimation of β_0, β_1, $\beta_2 \ldots . \beta_n$, the unknown parameters. The general method of estimation in logit regression that equates to the least squares function under the linear regression model is called *maximum likelihood*. The **maximum likelihood function** expresses the probability of the observed data as a function of the unknown parameters. Estimators of these parameters are those which maximize this function.

After estimating the coefficients, the covariates included in the model are assessed for significance (whether they are significantly related to the outcome variable). The estimate of the coefficient can be insignificant for two reasons: firstly the covariate has no effect on the outcome variable, or secondly, the dataset is too small, resulting in large error intervals incorporating zero. The estimate of the coefficient, β_1, represents the change in the logit for a change of one unit in the independent variable, x [Hosmer *et al*, 1989]. Where independent variables are dichotomous, β_1 is the log odds ratio. The odds ratio (Ψ) indicates how much more likely it is for the outcome to be present among those observations where $x = 1$, than among those where $x = 0$.

The odds ratio is derived from the estimate of the coefficient as expressed in equation 7.6.

$$\Psi = e^{\beta 1} \qquad (7.6)$$

Where x is a continuous variable, the odds ratio is derived in the same way. In this situation the odds ratio indicates, for a unit increase in x, how much more likely it is for the outcome to be present.

It is necessary to test whether the covariates included in the model are, in fact, independently related to the dependent variable [Kennedy, 1992]. To test the significance of a covariate, the log likelihood of the logit model containing the covariate (full model) is compared with the log likelihood of the model not containing it (reduced model), using a likelihood ratio test. If the p-value of this likelihood ratio test is more than 0.05 (according to assigned level of significance), then the reduced model is as good as the full model, and there is no advantage to including the covariate in the model.

When interaction between covariates is present, the association between one covariate and the dependent variable is modified by the level of another covariate [Hosmer *et al*, 1989]. Two-dimensional interaction can be assessed simply, prior to building the model, by producing a correlation table of the covariates [Kennedy, 1992]. The smaller the sample, the larger the correlation coefficient needs to be to indicate significant correlation. If the correlation between covariates exceeds the critical value for that population, there is interaction, which must be explicitly handled.

It is necessary to measure how effective the model is in describing the outcome variable. Complete assessment of the fitted model involves both

the calculation of summary measures of the difference in observed and predicted values and the individual components of these measures. A likelihood ratio test is used to measure the extent to which the restricted model fits the unrestricted model (that is, a model containing all possible covariates) [Hosmer *et al*, 1989]. However, unlike the R^2 value in linear regression, the aim is not simply to increase the 'p' value to as near unity as possible [Kennedy, 1992]. The predictive power of a logit model is assessed by running the model on a dataset other than the one from which it was derived. This method is frequently used in models built to predict survival. The following parameters can be derived from the data [Chang *et al*, 1988]:

***Specificity** (correct prediction of survival/%)*

$$= \frac{\text{PredAAlive}}{(\text{PredAAlive} + \text{PredDAlive})} \times 100$$

False positive rate = (1-specificity)x100

***Sensitivity** (correct prediction of death/%)*

$$= \frac{\text{PredDDead}}{(\text{PredDDead} + \text{PredADead})} \times 100$$

Overall correct prediction rate/%

$$= \frac{(\text{PredAAlive} + \text{PredDDead})}{\text{Total patients}} \times 100$$

Predictive value positive/% $= \frac{\text{PredDDead}}{\text{Total predicted to die}} \times 100$

Predictive value negative/% $= \frac{\text{PredAAlive}}{\text{Total predicted to live}} \times 100$

where:

PredAAlive = Predicted to live and lived

PredADead = Predicted to live but died

PredDAlive = Predicted to die but lived

PredDDead = Predicted to die and died.

If the model is run on the parent dataset (that is, the one from which it was derived), the parameters above can be derived to provide information on how well the model fits the data.

In summary, the aim in logit regression should be to derive a model that has the following characteristics:

1. the components of the model should exhibit individual significance ($p<0.05$);

2. correlation between covariates should be minimised ($\rho <$ criticalρ);

3. the model should not be significantly different from the unrestricted model (likelihood ratio test: $p>0.05$);

4. the model should be assessed to make sure it has *a priori* logic.

7.4.3 Logit Regression Analysis of Factors Affecting Six Month Mortality at LTH and DGH

This section outlines the logit regression analysis carried out on the LTH and DGH datasets to identify independent predictors of the six-month mortality. Firstly, the covariates listed in Tables 7.12a and 7.12b were

investigated individually to assess their unadjusted effect on six-month mortality. Table 7.12a reports patient admission characteristics that may affect six-month mortality. Table 7.12b reports recorded events occurring on ICU that may have an impact on six-month mortality. Three covariates recorded are proxies for organ failure (see section 7.3.3).

Table 7.12a Patient Admission Factors Associated with Six Month Mortality at DGH (n = 131) and LTH (n = 206)

Predicting factor	p (DGH)	p (LTH)
Sex	ns	ns
CANCER	ns	ns
ELECT	0.001↓	<0.00005↓
CPR	<0.0005↑	<0.00005↑
Age[1]	ns	ns
APACHE II[1]	ns	0.0022↑
CHRONIC	0.055↑	ns
CARDIAC	0.052↑	ns
IATRO	0.062↑	ns
VENT	ns	0.007↑
NEURO[2]	-	0.062↑
GENERAL[2]	ns	ns
VASCULAR[2]	0.012↑	0.032↓
TRAUMA[2]	ns	ns
OTHER[2]	0.024↓	ns
INFECT	0.031↑	0.029↑

[1] t-test. All other significance tests: χ^2; ns: $p \geq 0.10$

[2] significance with respect to the remaining surgical category 'medical'.

↑ Mortality increases in presence of risk factor

↓ Mortality decreases in presence of risk factor

Table 7.12b Events on ICU and Cost Parameters Associated with Six Month Mortality at DGH and LTH

Source	p (DGH)	p (LTH)
ICU length of stay	0.055↓	ns
Ventilated whilst on ICU	0.021↑	0.006↑
Dialysed whilst on ICU	ns	0.002↑
PA catheter whilst on ICU	ns	0.005↑
Pneumonia whilst on ICU	0.095↑	ns
ICU-acquired serious infection	0.100↑	ns
Total hospital stay	0.016↓	<0.00005↓
Variable patient cost/£	ns	ns
Variable patient day cost/£	ns	<0.00005↑

↑ Mortality increases in presence of risk factor

↓ Mortality decreases in presence of risk factor

From this initial analysis, it can be seen that some covariates appear to affect mortality at both centres, such as CPR prior to ICU admission or elective admissions. Other covariates have an impact at only one centre, such as APACHE scoring or presence of a cardiac condition. APACHE II has been validated for use in the UK as a severity of illness measure. The lack of a relationship demonstrated between it and mortality at DGH suggests measurement inaccuracies. ICU-acquired pneumonia has a marginally significant effect on mortality at DGH and none at all at LTH, when other factors have not been controlled for. Multiple logit regression

is necessary to examine whether this lack of relationship remains when the other factors are taken into account.

Logit regression models were derived for ICU, hospital and six month mortality at each centre. This was carried out to examine whether different factors were significant at different times, and whether ICU-acquired mortality was significant at different times. Only the models for six month mortality are reported in this chapter. This is because this is the most useful short term outcome measure, and the models for ICU and hospital mortality do not differ greatly from the models for six month mortality. The models derived for ICU and hospital mortality are summarised in Appendix 7.1. One model is described in detail to illustrate the analysis method.

7.4.3.1 Logit Regression Analysis of Six Month Mortality at LTH

This section outlines the logit regression analysis carried out on the LTH dataset to identify independent predictors of six-month mortality, using the methods described in section 7.4.2. The regression model derived is summarised in Table 7.13.

Table 7.13 Logit Regression on Factors Explaining Six Month Mortality at LTH

Source	Estimate (β_n)	Standard error of β_n	DF	χ^2	Ψ [3]	P
Intercept (β_0)	-4.270	0.970	1	19.36	0.01	<0.00005
PA catheter on ICU	0.436	0.198	1	4.87	1.55	0.0273
Hospital LOS 6-11 days[1]	-1.684	0.612	1	7.58	0.19	0.0059
Hospital LOS >11 days	-2.158	0.545	1	15.70	0.12	0.0001
Presence of cancer	0.729	0.214	1	11.63	2.07	0.0006
APACHE II[2] 16-18	0.594	0.276	1	4.61	1.81	0.0317
APACHE II 19-20	0.777	0.285	1	7.45	2.17	0.0063
APACHE II 21-26	1.626	0.559	1	8.45	5.08	0.0036
APACHE II 27-44	1.811	0.565	1	10.26	6.12	0.0014
Likelihood ratio	-	-	28	16.87	-	0.9510[4]

[1] Continuous variables converted to categories to reduce number of populations, categories compared with hospital LOS of less than 6 days.

[2] Continuous variables converted to categories to reduce number of populations, categories compared with APACHE II score 0-15.

[3] Log odds ratio

[4] $p>0.05$; therefore the restricted model is not significantly different from the unrestricted model

The model summarised in Table 7.13 shows that six month mortality of ICU patients at LTH is independently affected by insertion of a PA catheter whilst on ICU (indicating acute cardiac failure); their length of hospital stay; the presence of active cancer on admission and their acute severity of illness (APACHE II score). These factors all have a statistically significant ($p<0.05$) independent effect on mortality. Their effect is quantified by the odds ratio, Ψ, derived from the estimate of the coefficient, β_n, for each covariate. The risk of death at six months is increased by a factor of 1.55 if a PA catheter is inserted during the ICU stay. Compared with a hospital length of stay of less than six days, the risk of death decreases to 0.19 for a length of stay of 6 to 11 days, and decreases further to 0.12 for a length of hospital stay of more than 11 days. The presence of active cancer on ICU admission increases the six month risk of death by a factor of 2.07. Assuming that risk of death for patients with APACHE II scores less than sixteen is one, the higher APACHE score categories have increasingly higher risks of death as the score increases.

The model was run on the parent dataset to assess 'goodness-of-fit'. The results of this are summarised in Table 7.14. The predictive power of the model is not reported as this can only be determined by running the model on datasets other than that used to derive the model.

Table 7.14 Fit of Logit Model (Explanation of LTH 6 Month Mortality) to Parent Dataset

Model Parameter	Results of running logit on parent dataset (%)[1]
Sensitivity	100.0
Specificity	99.1
False positive rate	0.9[2]
Overall correct prediction rate	99.5

[1] If the model predicted that the patient had a 50% or greater chance of death at six months, this was taken to be a prediction of death.

[2] One patient predicted to die within 6 months of discharge, who lived.

ICU-acquired infections and pneumonias did not retain independent significance in logit regression. Mortality attributable to ICU-acquired pneumonia cannot therefore be assumed. When the logit models were run on a dataset only including ventilated patients, ICU-acquired pneumonia was still not independently significant.

7.4.3.2 Logit Regression Analysis of Six Month Mortality at DGH

This section outlines the logit regression analysis carried out on the DGH dataset to identify independent predictors of six-month mortality, using the methods described in section 7.4.2. The regression model derived is summarized in Table 7.15.

Table 7.15 Logit Regression on Factors Explaining Six Month Mortality at DGH

Source	Estimate (β_n)	Standard error of β_n	DF	χ^2	Ψ	P
Intercept (β_0)	0.667	0.339	1	3.87	1.95	0.0491
ELECT	-0.664	0.246	1	7.26	0.51	0.0070
APACHE II score >18[1]	0.535	0.221	1	5.85	1.71	0.0156
Hospital LOS >7 days[2]	-0.718	0.273	1	6.92	0.49	0.0085
Age > 50yrs [3]	0.739	0.289	1	6.56	2.09	0.0104
Likelihood ratio	-	-	7	4.83	-	0.6809

[1] Continuous variables converted to categories: category compared with APACHE 0-18

[2] Continuous variables converted to categories: category compared with LOS 0-7 days

[3] Continuous variables converted to categories: category compared with age up to 50 yrs.

The model summarised in Table 7.15 shows that six month mortality of ICU patients at DGH is independently affected by age; their length of hospital stay; whether they are an elective admission or not and their acute severity of illness (APACHE II score). Their effect is quantified by the odds ratio, Ψ, derived from the estimate of the coefficient, β_n, for each covariate. The risk of death at six months has an odds ratio of 0.51 if the patient is an elective admission. Compared with a hospital length of stay of less than eight days, the risk of death decreases to 0.49 for a length of stay of eight or more days. Patients with ages greater than 50 years on ICU admission have a six month risk of death that is 2.09 that of patients 50 years old or younger. Assuming that risk of death for patients with

APACHE II scores less than nineteen is one, the higher APACHE II score category has a 1.71 times higher risk of death. The use of dichotomous categorization in this model for APACHE scoring and length of hospital stay is attributable to the smaller patient group at DGH. In the case of APACHE II scores, it is also due to the probable lack of accuracy with which the scores have been collected.

The model was run on the parent dataset to assess 'goodness-of-fit'. The results of this are summarised in Table 7.16.

Table 7.16 Fit of Logit Model (Explanation of DGH Six Month Mortality) to Parent Dataset

Model Parameter	Results of running logit on parent dataset (%)[1]
Sensitivity	100.0
Specificity	97.6
False positive rate	2.4[2]
Overall correct prediction rate	98.5

[1] If the model predicted that the patient had a 50% or greater chance of death at six months, this was taken to be a prediction of death.

[2] Two patients who were predicted to die within six months of discharge, lived.

ICU-acquired infections and pneumonias did not retain independent significance in logit regression. Mortality attributable to ICU-acquired pneumonia cannot therefore be assumed. When the logit models were run on a dataset only including ventilated patients, ICU-acquired pneumonia

was still not independently significant.

7.4.3.3 Effect of Centre on Six-Month Mortality

The datasets from the two centres were combined to assess effects of centre on six-month mortality. The logit model derived from the LTH dataset was run on the combined dataset. The model is described in Appendix 7.2. The centre did not remain significant once centre-specific factors such as neurosurgery were controlled for. ICU-acquired pneumonia did not demonstrate significance.

7.5 DISCUSSION OF ANALYSIS FINDINGS

The principal aim of this analysis was to identify the impact on defined cost parameters of ICU-acquired pneumonia at two British ICUs in all ICU admissions and in ventilated admissions. The secondary aim was to identify whether the higher six month mortality at LTH could be explained by the higher ICU-acquired pneumonia rate. The isolation of increases in cost and mortality was complicated by the presence of other factors that could also have had an effect. This required the use of statistical techniques that allowed these other confounding factors to be controlled.

7.5.1 Analysis of Cost Parameters

The cost parameters investigated by this analysis were total variable cost, length of ICU stay and variable cost per patient day. These parameters were continuous dependent variables so linear regression was used to

isolate the effect of ICU-acquired pneumonia. The datasets used for this analysis were those collected and described in Chapter Six. Linear regression models were developed for both centres to explain the variation in variable cost, length of ICU stay and variable cost per patient day.

At LTH, the model derived to explain total variable cost explained 91.0% of the variation, suggesting a model that fit the data very well. Important factors were length of ICU stay, chronic health status, severity of illness of non-survivors and surgical speciality. It is unlikely that any important explanatory factors have been omitted from this model. At DGH, the equivalent model only explained 53.1% of the variation. This means that nearly half the variation in cost has not been explained by the model. It is suggested that this is due to incomplete retrieval of variable resource use at DGH. The only two factors remaining significant were length of ICU stay and dialysis whilst on ICU. Most of the explanatory power of the models at both centres is due to the correlation of variable cost with length of ICU stay. This correlation is stronger at LTH than at DGH, probably due to the improved data collection and also to increased regular treatment intensity at LTH. No impact on variable cost by ICU-acquired pneumonia was detected in either model. It was suggested that this was due to ICU-acquired pneumonia only affecting length of ICU stay, which would have been masked by these models.

Analysis of the datasets at both centres suggests that to better understand the factors explaining variation in variable cost, it is necessary to examine factors affecting length of ICU stay and variable cost per patient day separately. The regression model derived to explain length of ICU stay accounted for 51.1% of the variation at LTH and 45.6% at DGH. Models with similar ability to explain variation in length of ICU stay at the two centres were produced. The similarity must be partly due to the quality of

data collected being similar at the two centres, unlike the data on variable cost. Variation in length of ICU stay was attributed to dialysis whilst on ICU and insertion of a PA catheter whilst on ICU at LTH; sex and ventilation status at DGH; severity of illness, dying on the ICU, and occurrence of an episode of ICU-acquired pneumonia at both centres. Possible reasons why more of the variation was not accounted for are suggested organisational factors not measured by this analysis. These may include varying pressure for ICU beds determining discharge of some patients, availability of a bed on a ward to allow a patient to be discharged, ICU staffing levels affecting discharge rates or availability of senior medical staff to allow patient discharge. Analysis of both centres demonstrates that ICU-acquired pneumonia increases length of ICU stay by 113% in all LTH admissions, 116% in ventilated LTH admissions, 109% in all DGH admissions and 111% in ventilated DGH admissions. 95% confidence intervals for these values are listed in the model summaries.

Examination of factors affecting variable cost per patient day produced a regression model that was only able to explain 29.5% of the variation at LTH and 7.0% at DGH. The variable cost per patient day is a function of the total variable cost and length of ICU stay of that patient. Therefore, it is reasonable to assume that uncertainty around the factors causing variation in length of ICU stay have translated into these models. The low explanatory power of the DGH model in particular may be attributable to the poor variable cost data. The analysis of the LTH dataset suggests that an episode of ICU-acquired pneumonia increases variable cost per patient day modestly, by £53.3, in ventilated patients. The analysis of the DGH dataset shows no increase. This may be due to the absence of an increase or to the poor variable cost data.

As discussed in section 7.3.4, for economic analysis, the actual changes in

resource use due to an episode of ICU-acquired pneumonia in a ventilated patient are required. From the regression analyses reported the actual length of ICU stay and variable cost per patient day for ventilated patients who do and do not experience an episode of ICU-acquired pneumonia was not known. Therefore, it was necessary to derive these values for both centres. The analysis of the LTH dataset suggests that, in ventilated admissions, an episode of ICU-acquired pneumonia increases the length of ICU stay by 4.8 days and the total variable cost by £2660 (see Table 7.5 for ranges). Analysis of the DGH dataset suggests an increase in the length of ICU stay of 5.7 days and the total variable cost by £2060 (see Table 7.11 for ranges). Combination of this derived variable cost with fixed and staff costs associated with the ICU stay provided total costs per infected and uninfected patients for both centres. These values are required for economic evaluation of SDD.

The derived estimates of the impact of ICU-acquired pneumonia on length of ICU stay can be compared with the published evidence. The studies examining this are discussed in Chapter Three, section 3.3.1. Most studies used matched pairs to identify length of stay changes, and estimates range up to twenty days. Molina *et al* [1993] used the same method as reported in this analysis. The length of stay attributable to ICU-acquired pneumonia reported by them is 4.3 days, comparable with this study. No studies were found that reported the impact of ICU-acquired pneumonia on treatment intensity. It is reasonable to suggest that the incidence of pneumonia should have an effect on treatment intensity. However, in critically ill patients who are already receiving intense treatment, it is difficult to identify that incremental effect, especially if the retrieval of variable resource use is not reliable.

7.5.2 Analysis of Six Month Mortality

The secondary aim of this analysis was to identify whether the higher mortality at LTH could be attributed to ICU-acquired pneumonia. The analysis method used was logit regression because mortality is a dichotomous dependent variable. The mortality parameter examined was six-month mortality, considered to be the most useful short term mortality measure collected by this study. At LTH, the factors independently associated with mortality were length of hospital stay, severity of illness (as measured by APACHE II score), presence of active cancer on admission and acute cardiac failure requiring insertion of a PA catheter on ICU. At DGH, the factors identified were severity of illness, length of hospital stay, age and elective admission. The impact of these factors on mortality was expressed as odds ratios. The centre was not significant once the neurosurgery patients at LTH had been controlled for. Therefore, the case mix at LTH led to the higher mortality rate, rather than the higher incidence of ICU-acquired pneumonia.

Section 3.4.2 in Chapter Three discusses the published evidence for impact of ICU-acquired pneumonia on mortality. Studies containing much larger groups than the two analysed here were not able to demonstrate an independent association, so the inability of this analysis to do so is comprehendible.

7.6 CONCLUSIONS AND IMPLICATIONS FOR ECONOMIC EVALUATION

The aim of this analysis was to provide economic data for use in an economic analysis of SDD. The impact of ICU-acquired pneumonia on cost is necessary for this analysis. The data provided by this analysis quantifies

the economic impact of ICU-acquired pneumonia, from the ICU perspective. The data provided has been derived from datasets obtained from a district general hospital and a London teaching hospital. This will enable the economic analysis of SDD to be carried out, considering two different ICU environments.

The impact on total patient cost has been divided into the impact on ICU length of stay and on treatment intensity. A large increase in length of ICU stay has been detected at both centres, comparable with published evidence. A small increase in treatment intensity was detected at LTH only. Derived costs for infected and uninfected patients have been produced by this analysis. These figures are directly applicable to the decision-analytic model derived in Chapter Four. There are wide ranges around the point estimates from which the derived values are obtained. The effect of these on any conclusions drawn in the economic analysis must be investigated using sensitivity analysis.

The original decision-analytic model derived in Chapter Four (Figure 4.1) requires evidence on the life expectancy of post-ICU patients and the impact of ICU-acquired pneumonia on this life expectancy. Neither has been measured beyond six months in this study. Neither centre demonstrated an increase in any of the mortality parameters in the presence of ICU-acquired pneumonia. Therefore, it may either be assumed that the use of SDD to reduce the incidence of ICU-acquired pneumonia will have no effect on mortality, or that this study was not large enough to pick up the differences that do exist. In the former case, there will be no life-years gained as a result of the use of SDD. It is not possible to derive an incremental cost per life year gained. As no morbidity measures were collected to assess the impact of ICU-acquired pneumonia on quality of life, it is not possible to assess the incremental impact of SDD on quality of life.

Therefore, it is also not possible to derive incremental costs per QALY gained. In the latter case, it is necessary to return to published evidence for impact of ICU-acquired pneumonia on mortality.

In conclusion, the economic evidence reported in this chapter is British, current, based as closely on true economic costs as possible and patient-specific. This is a significant improvement over the economic evidence available for use in the secondary economic analysis of SDD. This evidence is expected to further improve the robustness of conclusions from Chapter Four.

Chapter 8: Economic Evaluation of SDD in Two British ICUs

8.1 INTRODUCTION

Chapter Four describes an economic evaluation of SDD, using published clinical and economic evidence. This economic evaluation concluded that SDD was a dominant therapy, as it was shown to improve patient outcomes at a reduced overall cost. This conclusion was also shown to be very robust, despite the significant uncertainty associated with many of the clinical and economic parameters. The parameters that were associated with most uncertainty, and could reverse the conclusion that SDD was dominant if varied, were base pneumonia rates, increase in length of ICU stay associated with pneumonia, cost per ICU day and increased therapeutic intensity associated with treating pneumonia. It was also suggested that the use of SDD regimens of differing cost affects the cost effectiveness of SDD. Empirical work reported in this thesis has aimed to reduce the uncertainty associated with these parameters. Chapter Five has provided practice information on the use of SDD in Britain. Chapters Six and Seven have provided primary economic evidence on the economic impact of ICU-acquired pneumonia on the cost of an ICU patient in two British ICU settings. The economic evaluation in this chapter applies this local economic and epidemiologic evidence to the decision-analytic pathway developed in Chapter Four. The theoretical cost effectiveness of SDD, if it were to be implemented at these two centres, is derived.

Section 8.2 outlines the aims and objectives of this analysis. The research question is defined in section 8.3. Sections 8.4 and 8.5 summarise the clinical and economic evidence for use in the economic analysis. Section 8.6 reports the incremental economic analysis for the

two centres. The sensitivity of the conclusions of the economic analysis to variation in clinical and economic parameters is considered in section 8.7. Section 8.8 investigates whether the use of primary stochastic economic data increases the robustness of conclusions, when compared with the secondary economic analysis reported in Chapter Four. The impact of centre-specific factors, such as occupancy and patient turnover rates, on the realisable cost savings from the implementation of SDD is examined in section 8.9. Finally section 8.10 examines the policy implications of this economic evaluation.

8.2 AIMS AND OBJECTIVES OF ECONOMIC EVALUATION OF SDD

The aim of this economic evaluation is to generate conclusions about the cost effectiveness of SDD if it were introduced into two British ICUs, using primary epidemiologic and stochastic economic evidence. The specific objectives of this analysis are:

1. to combine published clinical effectiveness data with primary epidemiologic and economic data to assess whether SDD can be demonstrated to be cost effective if introduced at either of the two centres;

2. to test the robustness of these conclusions using sensitivity analysis;

3. to examine whether the additional empirical evidence has increased the robustness of conclusions and

4. to examine what are the *realisable* clinical and economic implications of introducing SDD to the two centres, compared with the theoretical implications.

8.3 DEFINITION OF RESEARCH QUESTION

This economic evaluation assesses whether it would be cost effective to introduce SDD at two British ICUs. The two centres examined are a London teaching hospital (LTH) and a district general hospital (DGH) in the same geographical location. These are the two centres from the prospective resource use study reported in Chapter Six. The decision-analytic model developed in Chapter Four is used in the economic analysis of SDD at these two centres. This section describes the components of the research question.

8.3.1 Input to the Intervention

The input to the process of the intervention is the patient group. Literature review of SDD trials showed that the ICU patients most likely to receive SDD were ventilated adult admissions. The survey of British SDD users (Chapter Five) showed that ICU patients most likely to receive SDD were ventilated adult admissions. Therefore, as in Chapter Four, the target patient group is ventilated ICU admissions. This constitutes 89 patients at DGH and 171 patients at LTH.

8.3.2 Process of the Intervention

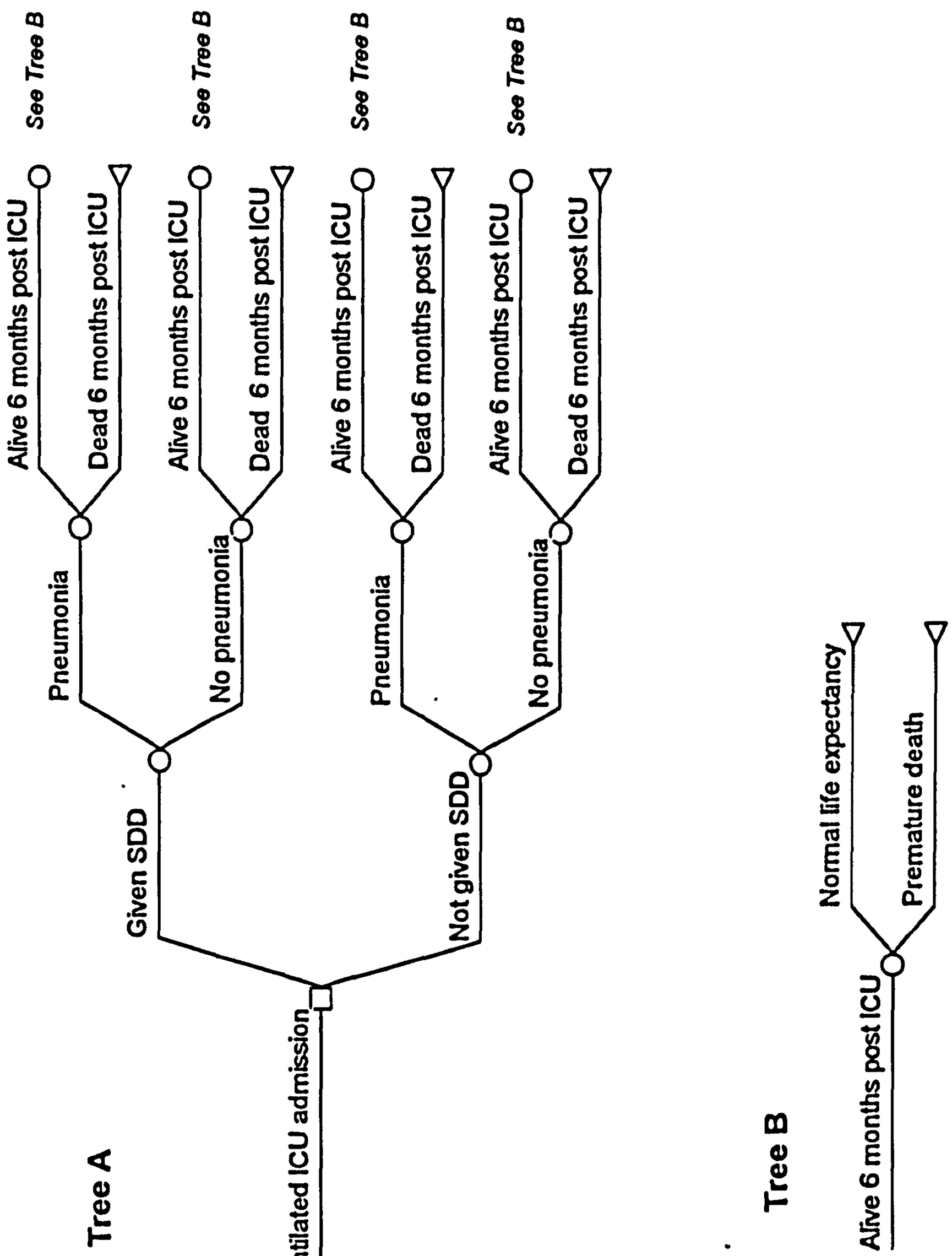
The intervention modelled to be undertaken at the two centres is the same process described in Chapter Four. The decision-based component of this process is the implementation of SDD. The probabilistic components are the occurrence of ICU-acquired pneumonia and short and long term mortality rates. The cost components are the implementation of the SDD regimen and maintenance of ICU-acquired pneumonia.

8.3.3 Output of the Intervention

The type of cost/outcome ratios derived depends upon the outcome measures used. The effect on clinical outcome of SDD is considered to be its effect on patient morbidity and mortality through its effect on ICU-acquired pneumonia incidence. If SDD is not shown to change patient outcomes, but cost only, then it becomes a cost minimisation analysis.

The input, process and outcome for the economic evaluation of SDD at LTH and DGH does not differ in principle from that in the economic evaluation in Chapter Four. Therefore, the structure of the decision-analytic model does not alter other than that the short term mortality measure is six month mortality instead of ICU mortality. This model is outlined in Figure 8.1.

Figure 8.1 Decision-Analytic Model for the Use of SDD on ICU



The clinical and economic evidence required for the decision-analytic model for each of the two study centres can be summarised into five categories:

1. the probability that the patient will contract ICU-acquired pneumonia with or without SDD;

2. the impact of ICU-acquired pneumonia and SDD on the short and long term mortality of the patient;

3. the impact of ICU-acquired pneumonia and SDD on the short and long term morbidity of the patient;

4. the impact of ICU acquired pneumonia and SDD on the resource use associated with the patient and

5. the unit costs associated with resource use.

The acquisition of clinical and economic evidence for these five categories is described in the next two sections.

8.4 ACQUISITION OF CLINICAL EVIDENCE

This section summarises the clinical evidence for use in the decision-analytic model. The evidence required is:

1. impact of SDD on ICU-acquired pneumonia rates at LTH and DGH;

2. short and long term mortality probability with or without ICU-acquired pneumonia at LTH and DGH;

3. impact of SDD and ICU-acquired pneumonia on quality of life at LTH and DGH.

8.4.1 Impact of SDD on ICU-acquired Pneumonia Rates at LTH and DGH

SDD only reduces the ICU-acquired pneumonia rate through its effect on Gram-negative late onset pneumonia. The probability of a ventilated ICU admission acquiring ICU-acquired pneumonia and Gram-negative late-onset pneumonia without the use of SDD was observed for each centre in the study reported in Chapter Six. These incidence rates are reported in Table 8.1 and are used in the economic evaluation. The 95% confidence intervals of the Gram-negative late-onset pneumonia rates are used as ranges for base pneumonia rates in the sensitivity analysis.

The effect of SDD on these ICU-acquired pneumonia rates is derived from the systematic review and meta-analysis of published clinical evidence in Chapter Four. The meta-analysis reported a 53% reduction (95% CI: 43% to 63%) in late onset Gram-negative pneumonia rate by SDD. Table 8.1 summarises the impact this would have on ICU-

acquired pneumonia rates and Gram-negative late onset pneumonia rates at the two centres. The probabilities of acquiring any pneumonia on the two ICUs are required for the decision-analytic pathways.

Table 8.1 Impact of SDD on ICU-Acquired Pneumonia Rates at LTH and DGH

Type of Pneumonia	Episodes per patient (LTH)		Episodes per patient (DGH)	
	No SDD	SDD	No SDD	SDD
Early onset	0.14	0.14	0	0
Late onset Gram+ve	0.19	0.19	0.11	0.11
Late onset Gram-ve	0.32[1]	0.15	0.17[2]	0.08
Overall ICU-acquired	0.65	0.48	0.28	0.19

[1] 95% CI of mean incidence rate: (0.23-0.41)

[2] 95% CI of mean incidence rate: (0.10-0.24)

The overall ICU-acquired pneumonia rate would be reduced from 65% to 48% at LTH and from 28% to 19% at DGH if SDD was introduced, assuming that SDD reduced Gram negative late-onset pneumonia by 53%. These theoretical reductions in pneumonia rate are used in the economic evaluation. The 95% confidence intervals (43% to 63%) quoted for this reduction are used in the sensitivity analysis to examine the effect of variation in SDD effectiveness on cost/outcome ratios. Trials have reported pneumonia rate reductions of less than 10% to 80%. To test for the impact of wider variation of effectiveness, these extremes are used as the sensitivity analysis ranges.

8.4.2 Impact of SDD on Short Term Mortality

In the economic evaluation of SDD in Chapter Four, the ICU mortality only was known. From the study of the two centres, the ICU, hospital and six month mortality is known for ventilated patients (Table 8.2).

Table 8.2 Summary of Ventilated Patient Mortality at LTH and DGH

Patient characteristic	DGH (n=89)	LTH (n=171)
% ICU mortality	18.0	26.9
% Hospital mortality	38.2	41.6
% 6 month mortality	40.7	50.3

However, logit regression analysis in Chapter Seven was not able to identify an independent effect of ICU-acquired pneumonia on any of these mortality parameters at LTH or DGH. This may be because ICU-acquired pneumonia does not have any effect on mortality. Alternatively, the patient group may have been too small to pick up any significant differences. In the absence of any other evidence it must be assumed for the base case economic evaluation that pneumonia does not affect mortality at either centre. If the reason for lack of detection was just due to group size, then it is necessary to examine the effect of an increase in mortality attributable to ICU-acquired pneumonia. Sensitivity analysis examines the situation where the mortality of patients receiving SDD is reduced through a reduction in pneumonia rates. The sensitivity ranges suggested are a lower limit of 0%, as observed in the empirical study and a higher limit of 10% (the value for mortality reduction by SDD derived by the meta-analysis in Chapter

Four). It is assumed, as in Chapter Four, that ICU-acquired pneumonia is extremely unlikely to be associated with a *decrease* in mortality rates.

8.4.3 Impact of SDD on Long Term Mortality

The ideal decision-analytic model (Figure 8.1) requires evidence on the life expectancy of post-ICU patients and the impact of ICU-acquired pneumonia on this life expectancy. Neither has been measured beyond six months in this study. If short term mortality is not assumed to be affected by ICU-acquired pneumonia or SDD and there is no evidence on the effect on long term mortality, then it is assumed for the base case economic evaluation that ICU-acquired pneumonia and SDD do not have an impact on long term mortality, so no incremental life years are gained by the use of SDD. For the purposes of sensitivity analysis, the effect of a 10% decrease in short term mortality is examined. In this situation, the theoretical effect on the overall long term mortality, and incremental LYGs, of the group is modelled. The same secondary data sources for LYGs are used as in the economic analysis in Chapter Four. The assumption made by Kerridge *et al* [1995] that the age-specific life-expectancy of ICU patients returns to 90% of the normal population is used. This assumption is used in this analysis to assess incremental cost per LYG. Any calculations also make the assumption, in the absence of evidence to the contrary, that ICU-acquired pneumonia has no other effect on long term mortality, as in the analysis in Chapter Four.

The ventilated patient groups at LTH and DGH have mean ages of 59.9 and 62.2 years, respectively. This would give an age-specific life expectancy of 19.2 years life expectancy (CSO Annual Abstract, 1991). Assigning 90% of these years to ICU survivors provides an estimate of 17.3 LYGs by ICU survivors in the model. The accuracy of this point

estimate is not known because it was not derived from the population to which it is being applied. To assess the impact of the variation of LYGs on the cost per LYG ratio, the LYGs by an ICU survivor are varied from 50% of the base value (8.7 LYGs) to 150% of the base value (26.0 LYGs), as in the analysis in Chapter Four.

8.4.4 Impact of SDD on Quality of Life and Utility

The observational study reported in Chapter Six did not assess the effect of ICU-acquired pneumonia on QoL or utility of ICU patients. If the assumption is made that ICU-acquired pneumonia has no effect on mortality, and there is no evidence on its effect on morbidity, it must be assumed, for the base case economic evaluation, that no QoL or utility was gained or lost. For the purposes of the sensitivity analysis where an effect on mortality is assumed, the theoretical impact on QoL and utility is modelled. The same secondary sources are used as in Chapter Four. Kerridge *et al* [1995] reported QALYs gained by ICU survivors. The base value for discounted QALYs (dQALYs, 5% discount rate) gained, taken from the Kerridge values, is 6.3 per ICU survivor, as this relates to the mean APACHE scores of the ventilated patients at the two centres. The ranges for sensitivity analysis are 0.8 to 9.9 dQALYs gained, to include patients with higher and lower APACHE scores, as in the analysis in Chapter Four.

Tables 8.3a and 8.3b summarise the clinical parameters required for the economic evaluation of SDD at LTH and DGH. The values derived from the literature and the observational study are listed, with their ranges for sensitivity analysis.

Table 8.3a Summary of Clinical Parameters, Their Associated Values and Ranges for Sensitivity Analysis at LTH

Clinical Parameter	No SDD	SDD	Incremental Effect Size due to SDD	Ranges for Sensitivity Analysis
Late-onset gram-negative pneumonia rate/%	32[1]	15	53%↓[2]	95% CI: 43-63↓ Extremes: 10-80↓
ICU Mortality/%	26.9	26.9	0	0 - 10↓
6 month mortality/%	50.3	50.3	0	0 - 10↓
Life Expectancy per ICU survivor/LYGs	17.3	17.3	0	8.7-26.0[4]
dQALYs per ICU survivor[3]	6.3	6.3	0	0.8- 9.9[4]

[1] Base pneumonia rate varied from 23 to 41%

[2] ↓ Indicates that there is a decrease in the parameter

[3] Discount rate 5%

[4] Sensitivity analysis ranges are used to vary these parameters for both SDD and non-SDD patients. There is no incremental effect attributable to ICU-acquired pneumonia or SDD.

Table 8.3b Summary of Clinical Parameters, Their Associated Values and Ranges for Sensitivity Analysis at DGH

Clinical Parameter	No SDD	SDD	Incremental Effect Size due to SDD	Ranges for Sensitivity Analysis
Late-onset Gram negative pneumonia rate/%	17[1]	8	53↓[2]	95% CI: 43-63↓ Extremes: 10-80↓
ICU Mortality/%	18.0	18.0	0	0 - 10↓
6 month mortality/%	40.7	40.7	0	0 - 10↓
Life Expectancy per ICU survivor/LYGs	17.3	17.3	0	8.7-26.0[4]
dQALYs per ICU survivor[3]	6.3	6.3	0	0.8- 9.9[4]

[1] Base pneumonia rate varied from 10% to 24%

[2] ↓ Indicates that there is a decrease in the parameter

[3] Discount rate 5%

[4] Sensitivity analysis ranges are used to vary these parameters for both SDD and non-SDD patients. There is no incremental effect attributable to ICU-acquired pneumonia or SDD.

8.5 ACQUISITION OF ECONOMIC EVIDENCE

This section summarises the economic evidence for use in the decision-analytic model. The cost consists of resource use and unit costs associated with that resource use. The two categories of resource use and unit costs are SDD implementation and treatment of ICU-acquired pneumonia. The costs incurred on ICU only are examined in this

economic analysis. Summaries of the economic data obtained for use in the revised economic evaluation are provided at the end of this section for both LTH and DGH.

8.5.1 Resource Use and Unit Costs Associated with SDD Implementation

The resource use and unit costs associated with the SDD regimen has three components. These are the drug treatment, the microbiological surveillance and the maintenance of side effects of SDD.

8.5.1.1 Resource Use Associated with SDD Pharmaceutical Regimen

The SDD pharmaceutical regimen modelled to be used by each centre in the event of implementing SDD is that reported most commonly used by British SDD users in the survey reported in Chapter Seven. The standard regimen proposed by Stoutenbeek *et al* [1984] and that used by the majority of published SDD studies is used most widely in Britain. Polymixin E, tobramycin and amphotericin (PTA) gel and liquid are reported to be used four times a day during the ICU stay. The gel is bought from a hospital pharmacy manufacturing unit. The constituents of the liquid are bought commercially. Intravenous cefotaxime 1g is used four times a day for the first three days. For each centre, the estimated theoretical costs of the SDD pharmaceutical regimen were derived from local drug acquisition, pharmacy overhead and administration costs. These costs are summarised in Table 8.4.

Table 8.4 Estimated Theoretical Cost of SDD Regimen at LTH and DGH Using Local Costs

Regime constituents	Cost at LTH/£	Cost at DGH/£
PTA Oral gel[1,2]	2.60	2.70
PTA Liquid[2]:		
Polymixin E 2mu qds	3.98	4.29
Tobramycin 80mg qds	12.08	19.96
Amphotericin 500mg qds	5.68	6.32
Cefotaxime 1g iv qds for 3 days	59.52	57.60

[1] Acquisition cost from BRI [1994]; pharmacy overhead cost added for each centre

[2] Cost per day

8.5.1.2 Cost of Microbiological Surveillance of SDD

Expected microbiological surveillance associated with SDD use is described in Chapter Four. The resource sparing, resource moderate and resource intensive surveillance programmes proposed in that evaluation are used in this economic analysis, substituting local costs for individual tests. Tables 8.5a and 8.5b summarise the estimated costs of these three models.

Table 8.5a Estimated Costs of Microbiological Surveillance at LTH

Model	Cost on admission/£	Cost during stay/£
Resource sparing	0	8.34 on suspicion of pneumonia
Resource moderate	15.30	15.30 every 3rd day
Resource intensive	27.82	23.64 every 3rd day

Table 8.5b Estimated Costs of Microbiological Surveillance at DGH

Model	Cost on admission/£	Cost during stay/£
Resource sparing	0	9.00 on suspicion of pneumonia
Resource moderate	18.00	18.00 every 3rd day
Resource intensive	37.00	27.00 every 3rd day

8.5.1.3 Cost Associated with the Maintenance of Side Effects Arising from SDD

As there is no evidence to the contrary, it is assumed that there are no complications associated with the use of SDD, including outbreaks of antibiotic-resistant bacteria.

The SDD regimen selected for use in the economic evaluation is summarised in Tables 8.6a and 8.6b. This is referred to as the 'resource moderate' regimen at each centre. To assess the effect of more or less intensive SDD regimens on cost/outcome ratios, a 'resource sparing' and a 'resource intensive' model are also summarised in the table. These models have the same components as those used in the economic evaluation in Chapter Four. The resource sparing regimen uses daily PTA, the lowest level of microbiological surveillance and no cefotaxime. The resource intensive regimen uses the highest level of microbiological surveillance, cefotaxime and daily PTA. The impact of these models is examined in the sensitivity analysis.

Table 8.6a Summary of SDD Regimens Proposed for Use in Economic Evaluation at LTH

Component of Regimen	Resource Sparing Regimen	Resource Moderate Regimen	Resource Intensive Regimen
Cost of PTA gel and liquid per day/£	24.34	24.34	24.34
Cost of Cefotaxime 1g iv qds for 4 days/£	-	59.52	59.52
Cost of microbiological surveillance on admission/£	0	15.30	27.82
Cost of microbiological surveillance twice a week/£	8.34[1]	15.30	23.64

[1] On suspicion of pneumonia only

Table 8.6b Summary of SDD Regimens Proposed for Use in Economic Evaluation at DGH

Component of Regimen	Resource Sparing Regimen	Resource Moderate Regimen	Resource Intensive Regimen
Cost of PTA gel and liquid per day/£	33.27	33.27	33.27
Cost of Cefotaxime 1g iv qds for 4 days/£	-	57.60	57.60
Cost of microbiological surveillance on admission/£	0	18.00	37.00
Cost of microbiological surveillance twice a week/£	9.00[1]	18.00	27.00

[1] On suspicion of pneumonia only

8.5.2 Resource Use and Unit Costs Associated with ICU-Acquired Pneumonia

Resource use resulting from ICU-acquired pneumonia can be divided into two parts. The first is the resultant increase in stay on the ICU and increase of overall hospital stay. The second is the increase in treatment resulting from pneumonia. The unit costs required are those associated with a day's stay on ICU and with treating an episode of pneumonia. The prospective study reported in Chapter Six identified cost independently associated with ICU-acquired pneumonia in ventilated patients at the two centres. Tables 8.7a and 8.7b summarise the impact of ICU-acquired pneumonia on cost at LTH and DGH, derived from the regression analysis in Chapter Seven.

Table 8.7a Ranges of Parameters Required for Economic Analysis for the LTH Dataset

Parameter for Use in Economic Analysis	Base case value	Ranges for Sensitivity Analysis
Increase in length of ICU stay due to pneumonia derived from linear regression/%	116	88-144%
Length of stay of uninfected patient/days[1]	4.1	3.7, 4.6
Length of stay of patient with ICU-acquired pneumonia/days[1]	8.9	8.7, 9.2
Increase in variable cost per patient day due to pneumonia derived from linear regression/£	53.3	2.4-101.3

[1] Uninfected and infected lengths of stay derived from 88% increase in length of ICU stay are 4.6 and 8.7 days respectively. Uninfected and infected lengths of stay derived from 144% increase in length of ICU stay are 3.7 and 9.2 days respectively.

Table 8.7b Ranges of Parameters Required for Economic Analysis for the DGH Dataset

Parameter for Use in Economic Analysis	Base case value	Ranges for Sensitivity Analysis
Increase in length of ICU stay due to pneumonia derived from linear regression/%	111	78-144%
Length of stay of uninfected patient/days[1]	5.2	4.9, 5.5
Length of stay of patient with ICU-acquired pneumonia/days[1]	10.9	9.8, 11.9
Increase in variable cost per patient day due to pneumonia derived from linear regression/£	0	0[2]

[1] Uninfected and infected lengths of stay derived from 78% increase in length of ICU stay are 5.5 and 9.8 days respectively. Uninfected and infected lengths of stay derived from 144% increase in length of ICU stay are 4.9 and 11.9 days respectively.

[2] Mean variable cost per patient day is £362.4. 95% CI: £4.8 to £720.0.

8.5.3 Summary of Cost of Patients for Economic Evaluation of SDD at LTH and DGH

This section has listed all the economic parameters required for the economic evaluation of SDD, with justified ranges for sensitivity analysis. For both centres, the cost of treating a ventilated admission, whether they suffer an episode of ICU-acquired pneumonia or not, has been reported. An estimated theoretical cost of SDD implementation has also been reported. The combination of these two categories of cost enables a theoretical cost to be derived for treating those patients if SDD were implemented. Those derived costs are reported in Table 8.8 and are used in the base case cost/outcome analysis reported in section 8.6. Values of the economic parameters are varied according to the ranges reported in this section for sensitivity analysis in section 8.7.

Table 8.8 Summary of Patient Costs at LTH and DGH for Base Case Economic Evaluation of SDD

Ventilated patient subgroup	Cost per patient at DGH/£	Cost per patient at LTH/£
No SDD, no ICU acquired pneumonia	5207	4199
No SDD, ICU acquired pneumonia	10915	9584
SDD, no ICU acquired pneumonia	5489	4395
SDD, ICU acquired pneumonia	11421	9921

8.6 INCREMENTAL ECONOMIC ANALYSIS OF SDD AT LTH AND DGH

In this section, the incremental costs and outcome changes that would occur if SDD were implemented at DGH and LTH were derived. This was carried out by attaching the epidemiologic, clinical and economic data to the decision-analytic model for each centre. A 'base case' model was produced using clinical and economic point estimates. Firstly, clinical probabilities were attached to the decision-analytic model, from Tables 8.3a and b, for each of the two centres, as shown in Figures 8.2a and 8.2b. It was still not possible to attach clinical probabilities to Tree B because there was no available evidence on the effect of pneumonia or SDD on life expectancy from the empirical study.

Figure 8.2a: Decision-Analytic Model of SDD, Including Clinical Probabilities at LTH

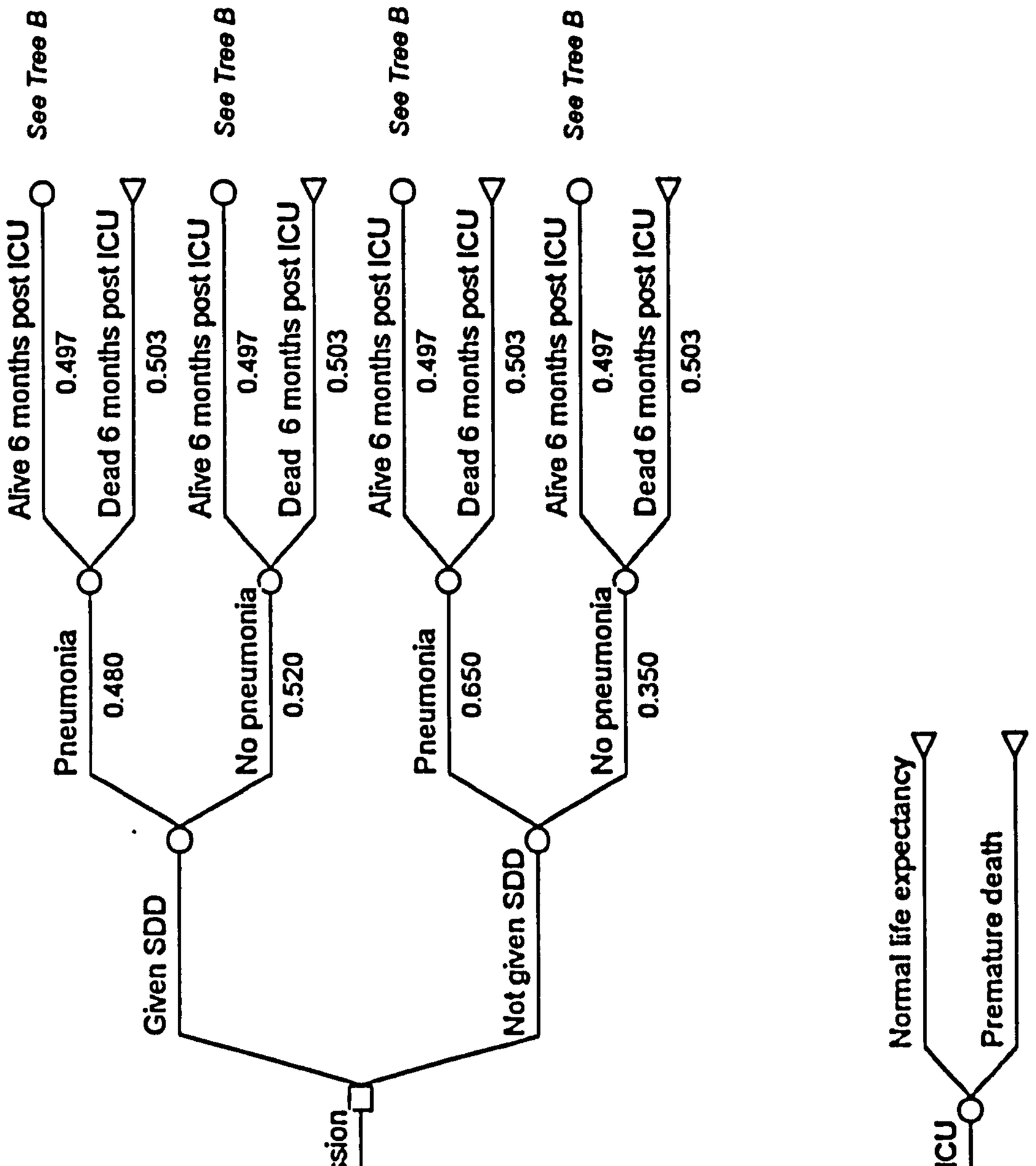
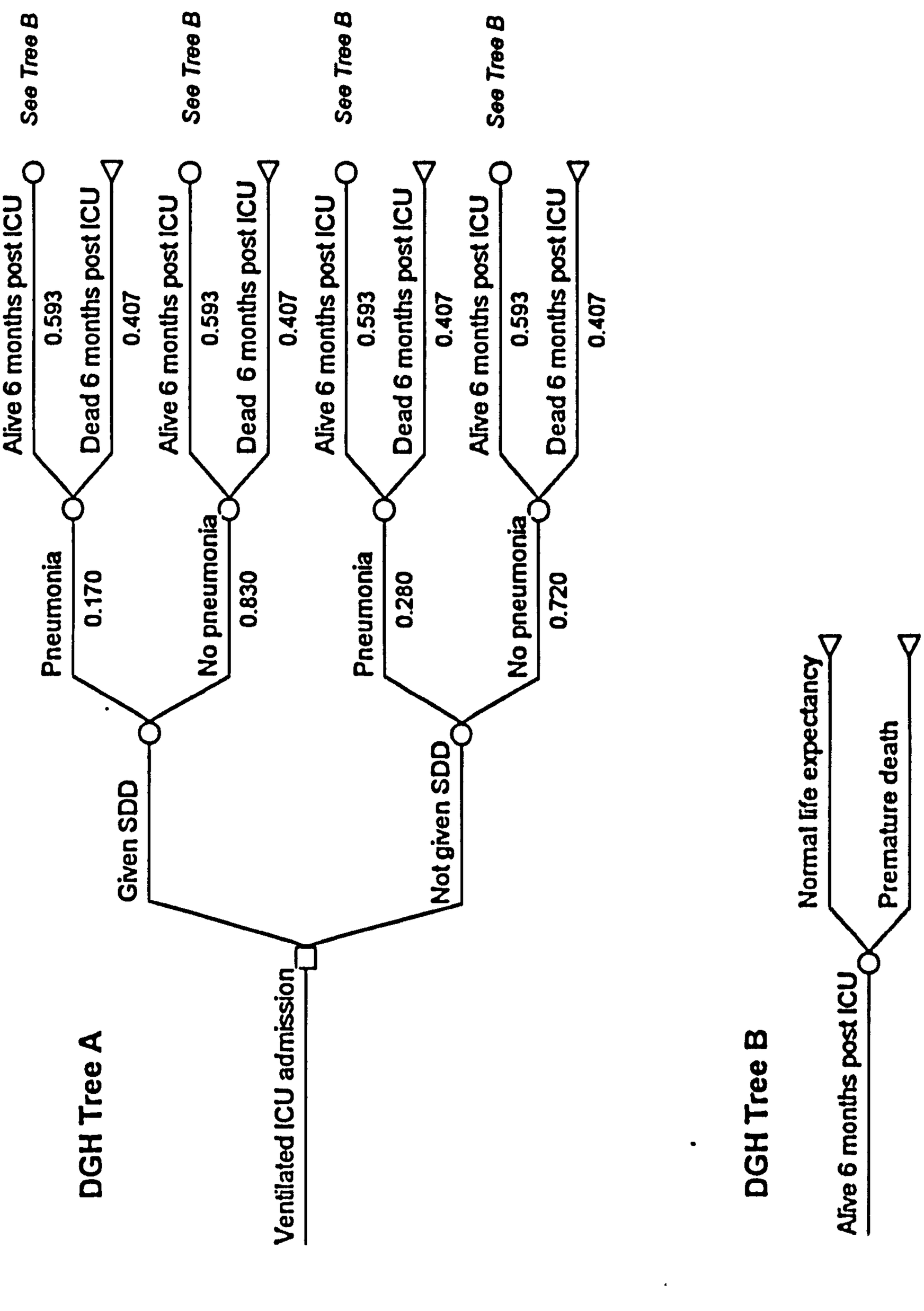


Figure 8.2b: Decision-Analytic Model of SDD, Including Clinical Probabilities at DGH



The economic data was also attached to the decision-analytic models, as summarised in Table 8.8. Incremental economic analyses were carried out for both centres. They are considered separately below.

8.6.1 Incremental Economic Analysis at LTH

At LTH, 171 ventilated patients were admitted to ICU during the study period. They had a 65% chance of contracting an episode of ICU-acquired pneumonia which included a 32% chance of contracting a Gram-negative late onset pneumonia. If infected, they cost the ICU £9584 each and had a 50.3% chance of dying in the following six months. If they did not contract pneumonia, they cost the ICU £4199 each and still had a 50.3% chance of dying in the following six months. The six month survivors were assumed to have gained 17.3 LYGs and 6.3 dQALYs each. For the SDD arm of the model, these 171 patients were modelled to receive SDD. They therefore would have had a 48% chance of contracting ICU-acquired pneumonia, including a 17% chance of contracting Gram-negative late onset pneumonia. Infected and uninfected patients would have cost the ICU £9921 and £4395, respectively. They would have had the same outcomes as the patients who do not receive SDD.

Without the use of SDD, 111 patients contracted pneumonia and 86 died in the following six months, at a total cost of £1.317×10^6. The 85 survivors theoretically gained 1470.5 LYGs and 535.5 dQALYs in total.

If the 171 patients were treated with SDD from ICU admission, 82 would have contracted pneumonia and 86 would have died in the following six months at a cost of £1.205×10^6. The 85 survivors gained 1470.5 LYGs and 535.5 QALYs in total. The overall incremental *decrease* in cost associated with the patients who receive SDD would have been £0.11×10^6. This decrease in cost would have been

associated with 29 fewer episodes of pneumonia, no fewer ICU deaths, or additional LYGs or added dQALYs. The inference is that SDD is the *dominant* therapy. If reduction in pneumonia rate is assumed to an intermediate outcome, then there is no change in ultimate patient outcome associated with SDD. Therefore this analysis becomes a cost minimisation analysis. The therapy is still dominant because the use of SDD results in an overall reduction in *cost per six month survivor* of £1307. This analysis is reported in Table 8.9a.

8.6.1 Incremental Economic Analysis at DGH

At DGH, 89 ventilated patients were admitted to ICU during the study period. They had a 28% chance of contracting an episode of ICU-acquired pneumonia which included a 17% chance of contracting a Gram-negative late onset pneumonia. If infected, they cost the ICU £10915 each and had a 40.7% chance of dying in the following six months. If they did not contract pneumonia, they cost the ICU £5207 each and still had a 40.7% chance of dying in the following six months. The six month survivors were assumed to have gained 17.3 LYGs and 6.3 dQALYs each. For the SDD arm of the model, these 89 patients are modelled to receive SDD. They therefore would have had a 19% chance of contracting ICU-acquired pneumonia, including an 8% chance of contracting Gram-negative late onset pneumonia. Infected and uninfected patients would have cost the ICU £11421 and £5489, respectively. They would have had the same outcomes as the patients who do not receive SDD.

Without the use of SDD, 25 patients contracted pneumonia and 36 died in the following six months, at a total cost of £6.057×10^5. The 53 survivors gained a theoretical 916.9 LYGs and 333.9 dQALYs in total. If the 89 patients were treated with SDD from ICU admission, 17 would

have contracted pneumonia and 36 would have died in the following six months at a cost of £5.888x10^5. The 53 survivors would have gained 916.9 LYGs and 333.9 dQALYs in total. The overall incremental *decrease* in cost associated with the patients who receive SDD would have been £0.17x10^5. This decrease in cost would have been associated with 8 fewer episodes of pneumonia, no fewer ICU deaths, or additional LYGs or added dQALYs. The inference is that SDD is the *dominant* therapy. If a cost minimisation analysis is carried out, the therapy is still dominant because the use of SDD would result in an overall reduction in cost per six month survivor of £319. This analysis is reported in Table 8.9b.

Table 8.9a Incremental Cost Effectiveness Analysis of SDD in ICU-Acquired Pneumonia Prevention at LTH

Strategy	Data			Incremental Comparison	Change in Outcome Measures by SDD			
	Cost/171 (£)	Infections /171	Deaths /171	Cost/£	Infections prevented	Lives saved	LYGs	dQALYs gained
No SDD	1316572	111	86	-	-	-	-	-
SDD	1205441	82	86	-111131	29	0	0	0

No SDD: For 171 patients, 111 contract infection at cost of £9584 per patient

60 do not, at a cost of £4199 per patient. Total cost = (111x9584) + (60x4199) = $£1.317 \times 10^6$

Cost per six month survivor: £15489

SDD: For 171 patients, 82 contract infections at a cost of £9921 per patient

89 do not, at a cost of £4395 per patient. Total cost = (82x9921) + (89x4395) = $£1.205 \times 10^7$

Cost per six month survivor: £14182

Reduction in cost per six month survivor: £1307

Table 8.9b Incremental Cost Effectiveness Analysis of SDD in ICU-Acquired Pneumonia Prevention at DGH

Strategy	Data			Incremental Comparison	Change in Outcome Measures by SDD			
	Cost/89 (£)	Infections /89	Deaths /89	Cost/£	Infections prevented	Lives saved	LYGs	dQALYs gained
No SDD	605666	25	36	-	-	-	-	-
SDD	588751	17	36	-16915	89	0	0	0

No SDD: For 89 patients, 25 contract infection at cost of £10915 per patient

64 do not, at a cost of £5207 per patient. Total cost = (25x10915) + (64x5207) = £6.057×10^5

Cost per six month survivor: £11428

SDD: For 89 patients, 17 contract infections at a cost of £11421 per patient

72 do not, at a cost of £5489 per patient. Total cost = (17x11421) + (72x5489) = £5.888×10^5

Cost per six month survivor: £11109

Reduction in cost per six month survivor: £319

8.7 SENSITIVITY ANALYSIS

The conclusions from the economic analyses that SDD is dominant at the two centres only hold for the conditions defined in the base cases. It is necessary to test the sensitivity of this dominance at the two centres to variation in underlying parameters. The ranges of the variation of the parameters are used as outlined in sections 8.4 and 8.5. The parameters examined are variation in SDD effectiveness in reducing pneumonia rates; base pneumonia rates; pneumonia-attributable mortality; cost of different SDD regimens; increased length of ICU stay due to pneumonia and costs associated with pneumonia treatment.

8.7.1 Effect of Changing Decrease in Pneumonia Rate by SDD

The reduction in ICU-acquired pneumonia rate by SDD is 53% (95% CI: 43% to 63%). The sensitivity analysis examines the impact of variation of SDD effectiveness on the conclusion that SDD is dominant, at both ICUs. However, reported reductions in pneumonia rate by SDD range from 10 to 80%, so the effect of this amount of variation is also examined. Table 8.10 summarises the effect that these variations in reduction in pneumonia rate have on cost per pneumonia avoided and cost per six month survivor. Figures 8.3 and 8.4 illustrate the impact on cost per pneumonia avoided and cost per six month survivor of changing the decrease in pneumonia rate, in stages from 10% to 80%. The base case (B) where there is 53% reduction and the low (L) and high (H) limits of the 95% confidence intervals are marked on the graph.

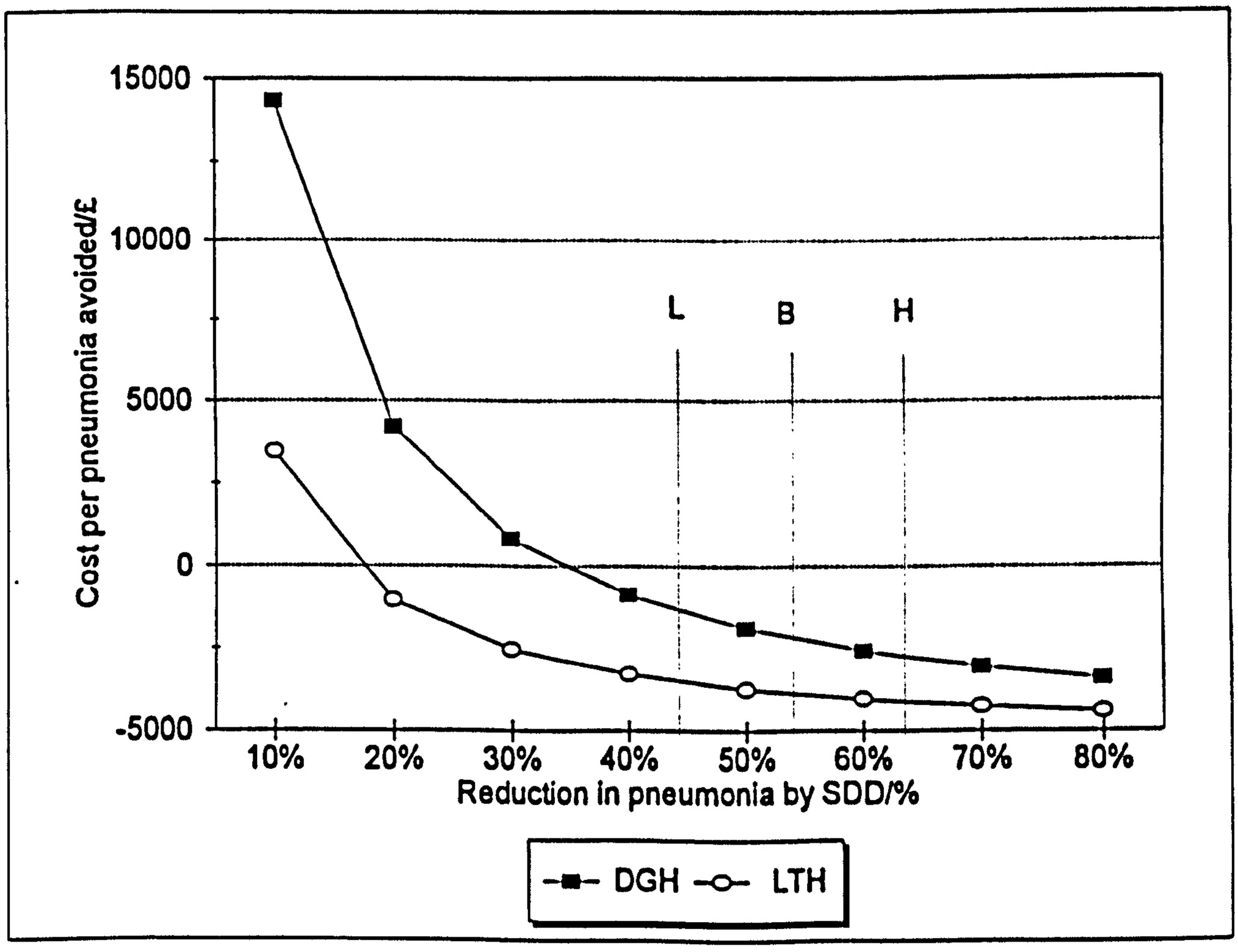
This sensitivity analysis suggests that SDD is dominant at both centres within the 95% confidence intervals of effectiveness. Therefore, the conclusion that SDD is dominant at LTH and DGH is insensitive to the effectiveness of SDD. SDD becomes the dominant therapy at DGH

where it reduces pneumonia rates by at least 34%. In comparison, SDD becomes the dominant therapy at LTH where it reduces pneumonia rates by at least 18%. It is suggested that this difference can be attributed to the higher ICU-acquired pneumonia incidence at LTH. The analysis in Chapter Four showed that a higher base pneumonia rate increased the cost effectiveness of SDD.

Table 8.10 Effect of Variation of Reduction in Pneumonia Rates by SDD on Cost/Outcome Ratios at Both Centres

Upper and lower limit of sensitivity analysis and base value of SDD efficacy	Incremental cost/£	
Cost per pneumonia avoided	DGH	LTH
↓10% pneumonia rate by SDD	14327	3454
↓53% pneumonia rate by SDD	-2109	-3832
↓80% pneumonia rate by SDD	-3399	-4404
Incremental cost per six month survivor		
↓10% pneumonia rate by SDD	2167	1178
↓53% pneumonia rate by SDD	-319	-1307
↓80% pneumonia rate by SDD	-514	-1502

Figure 8.3 Graph to Show Effect of Variation of SDD Efficacy on Incremental Cost per Pneumonia Avoided at DGH and LTH

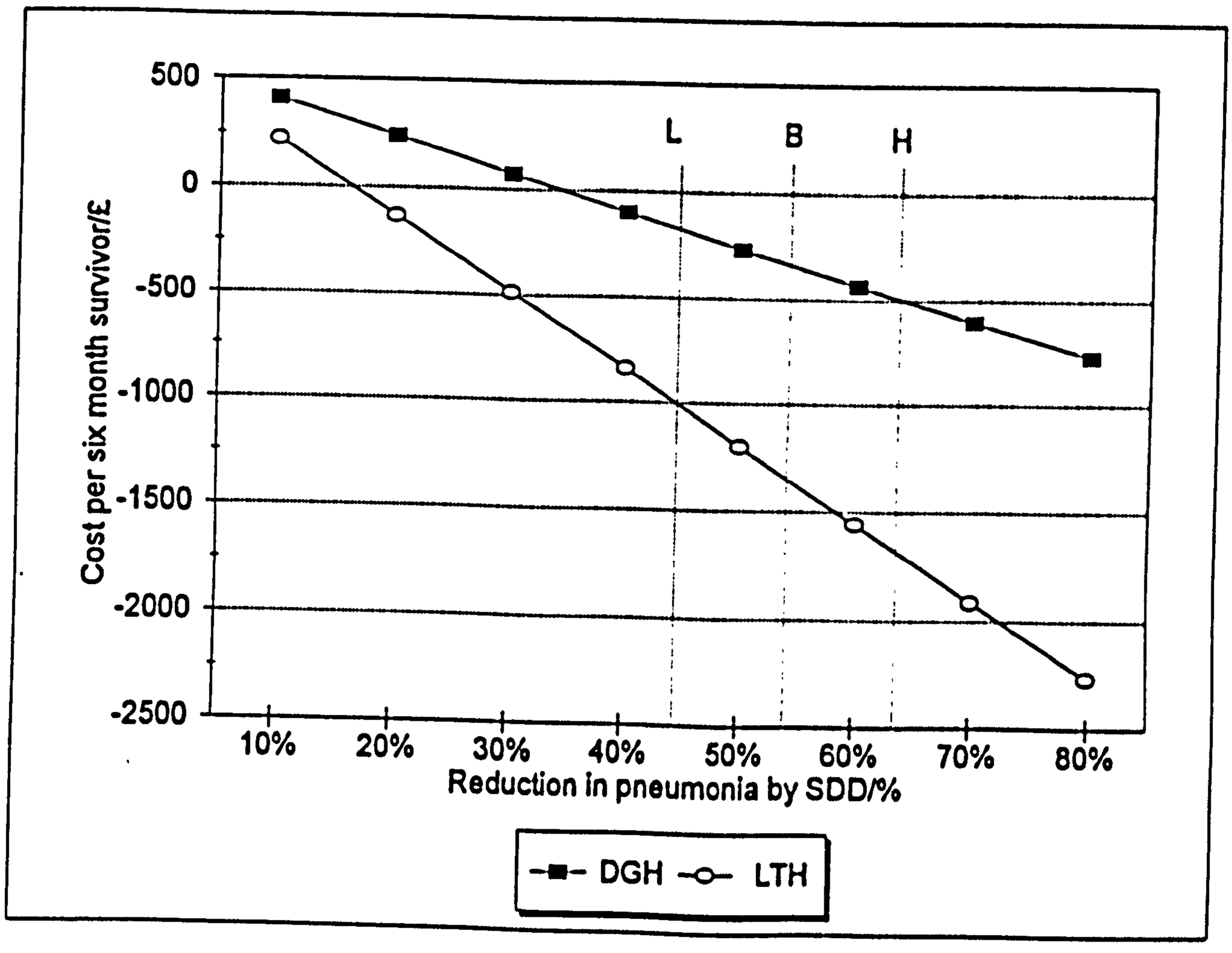


L: Low estimate for decrease in pneumonia rate (43%)

B: Base estimate for decrease in pneumonia rate (53%)

H: High estimate for decrease in pneumonia rate (63%)

Figure 8.4 Graph to Show Effect of Variation of SDD Efficacy on Incremental Cost per Six Month Survivor at DGH and LTH



L: Low estimate for decrease in pneumonia rate (43%)

B: Base estimate for decrease in pneumonia rate (53%)

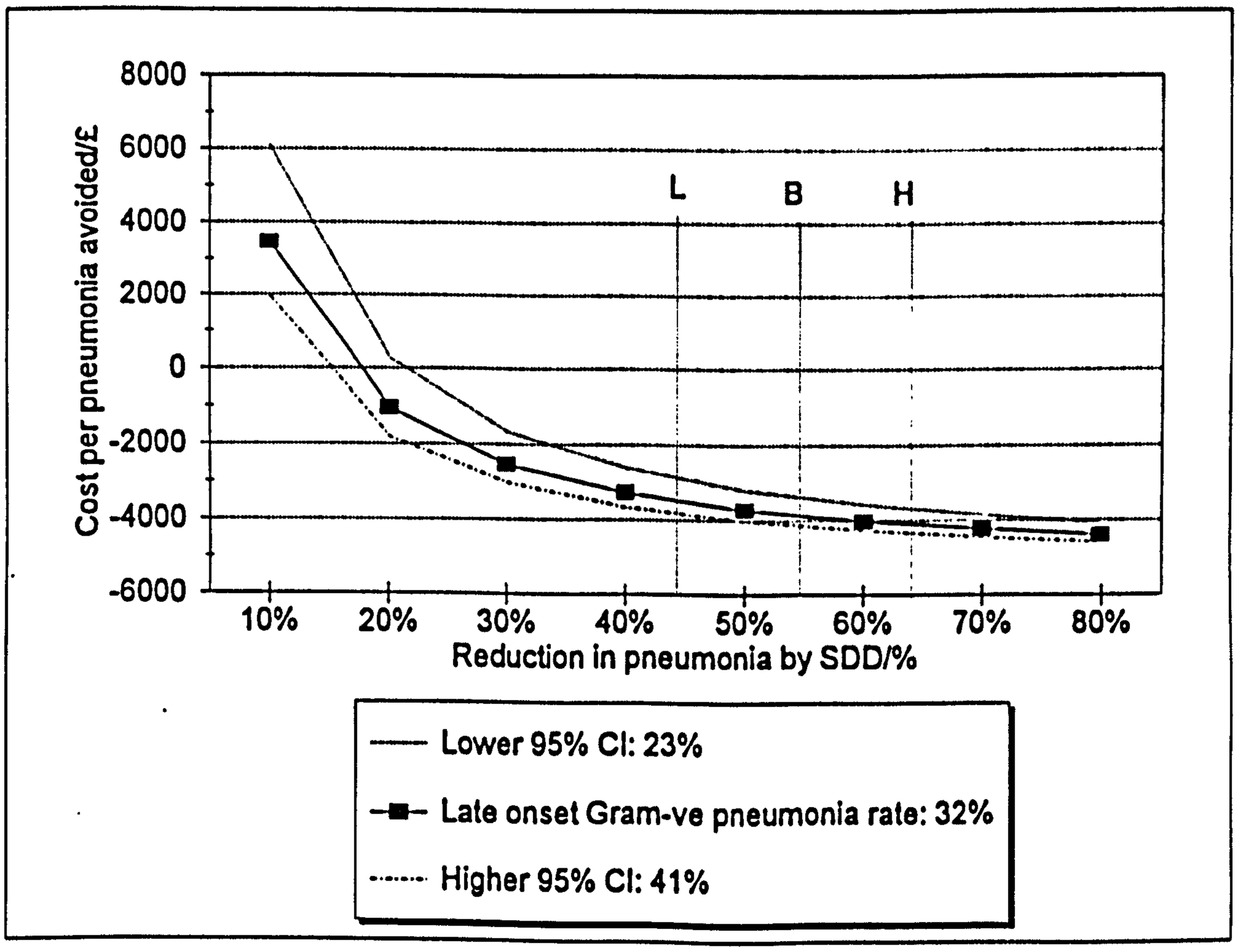
H: High estimate for decrease in pneumonia rate (63%)

8.7.2 Effect of Changing Base Pneumonia Rate

The base ICU-acquired and Gram-negative late onset pneumonia rates are known for both centres. It is known from the analysis in Chapter Four that this parameter significantly affects the cost effectiveness of SDD. The higher the base pneumonia rates are, the more cost effective SDD can be. The ICU-acquired and Gram-negative late onset pneumonia rates are 65% and 32% at LTH, and 28% and 17% at DGH. These observed values were derived empirically and have 95% confidence intervals. Therefore, the *cost per pneumonia avoided* curves in Figure 8.3 are actually more accurately represented as bands, with the boundaries defined by the 95% confidence intervals of the incidence rates. This is represented graphically for each centre in Figures 8.5a and 8.5b. The bands are narrow at both centres, due to the narrow 95% confidence intervals around the pneumonia incidences.

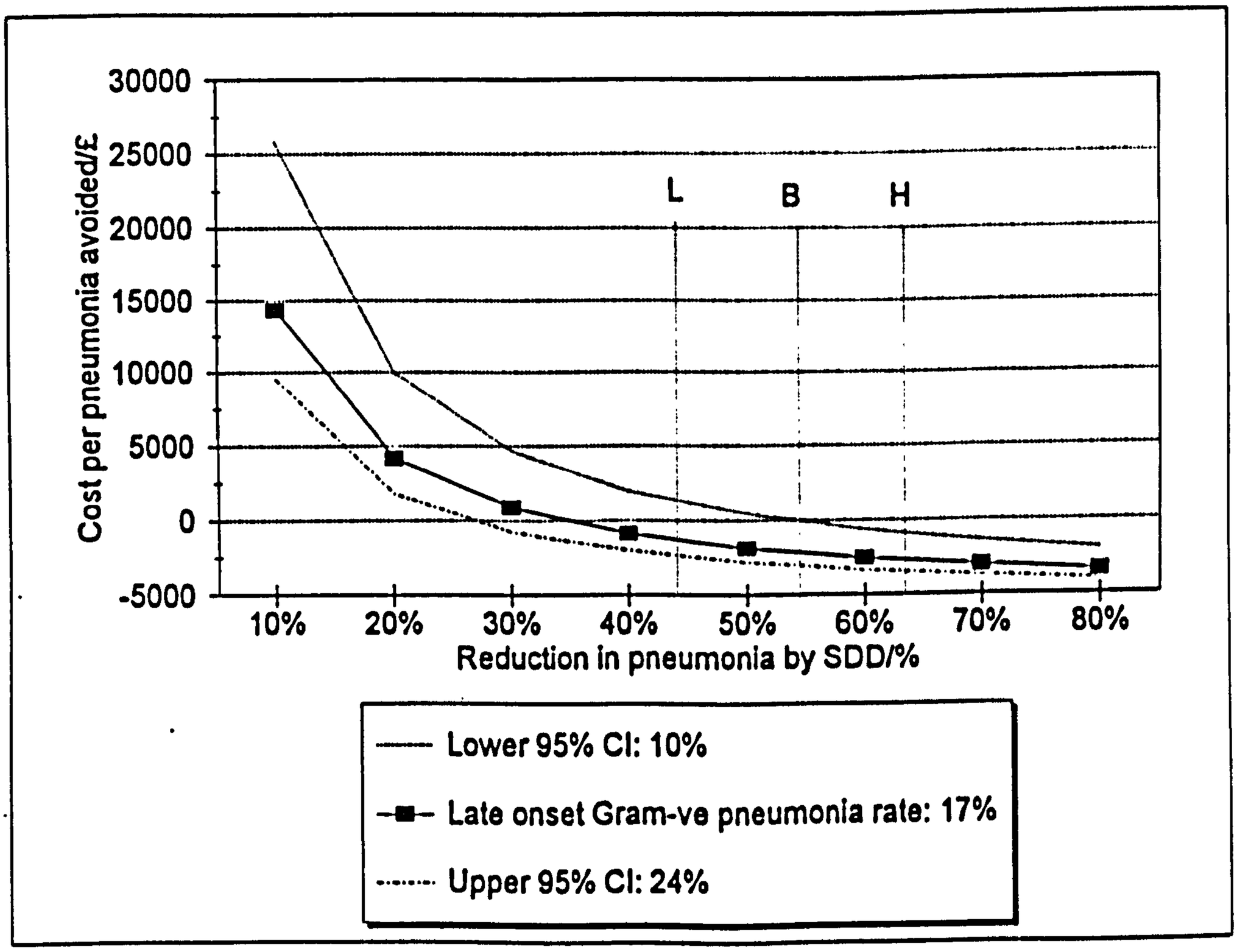
The conclusion that SDD is dominant at LTH is not changed within these ranges. However, the conclusion that SDD is dominant at DGH is not robust to variation in base pneumonia rates. Figure 8.5b shows that at the lower 95% confidence interval where the base pneumonia rate is 10%, SDD loses dominance. This reinforces the conclusions made in Chapter Four that the cost effectiveness of SDD is very sensitive to base pneumonia rates.

Figure 8.5a Effect of Variation of SDD Efficacy on Incremental Cost per Pneumonia Avoided at LTH (including 95% confidence intervals for base pneumonia rate)



- *L: Low estimate for decrease in pneumonia rate (43%)*
  B: Base estimate for decrease in pneumonia rate (53%)
  H: High estimate for decrease in pneumonia rate (63%)

Figure 8.5b Effect of Variation of SDD Efficacy on Incremental Cost per Pneumonia Avoided at DGH (including 95% confidence intervals for base pneumonia rate)



L: Low estimate for decrease in pneumonia rate (43%)

B: Base estimate for decrease in pneumonia rate (53%)

H: High estimate for decrease in pneumonia rate (63%)

8.7.3 Effect of Changing Mortality Effects of Pneumonia

The base case models for both centres assumed that ICU-acquired pneumonias did not increase mortality. This sensitivity analysis examines the impact of an increase in mortality associated with pneumonia and the associated reduction in mortality in the SDD-treated group. The number of deaths averted by SDD (and thus LYGs and dQALYs gained) is entirely dependent upon the magnitude of the reduction in pneumonia rate. The change in cost due to the implementation of SDD is not affected. SDD is dominant at both centres, so any deaths averted occur in conjunction with a reduction in cost. If mortality is not reduced by SDD there will be no deaths averted and no associated LYGs or QALYs gained at either centre. If the mortality were reduced by 10%, there would be 8.5 deaths averted at six months after ICU discharge, 147.7 LYGs and 53.8 dQALYs gained at LTH. The cost reduction would still be £111131. Similarly, at DGH, there would be 3.4 deaths averted at six months after ICU discharge, 58.5 LYGs and 21.3 dQALYs gained. The cost reduction would still be £16905. This sensitivity analysis implies that, in a time period of eleven months, at least eight lives could have been saved at LTH and three at DGH if SDD were implemented, along with the associated LYGs and dQALYs gained. However, this is based on the assumption that, in reducing pneumonia rates, SDD also reduces mortality. This has not been unequivocally proven, so these results can only be tentatively supported.

The second area of uncertainty here is the precision of the estimates for LYGs and dQALYs. The values for LYGs and dQALYs are very tentative due to their sources, discussed in Chapter Four. The significant uncertainty surrounding these values is reflected in their wide, and largely arbitrary, ranges for sensitivity analysis. The sensitivity ranges selected for LYGs (8.7 to 26.0) and dQALYs gained (0.8 to 9.9) from

Tables 8.3a and 8.3b are used to derive ranges for these outcome measures. The results of this analysis are reported in Tables 8.11a and 8.11b.

However, the uncertainty around these outcome parameters does not change the conclusion that SDD is dominant at both centres, so the conclusions are insensitive to the variation arising from this uncertainty.

Table 8.11a Effect of the Assumption that SDD Causes a 10% Reduction in Six Month Mortality at LTH

Outcome parameter	Units of outcome gained	Sensitivity Analysis Range
Deaths averted at six months	8.5	-
LYGs	147.7	74.3-222.0
dQALYs gained	53.8	6.8-84.6

Table 8.11b Effect of the Assumption that SDD Causes a 10% Reduction in Six Month Mortality at DGH

Outcome parameter	Units of outcome gained	Sensitivity Analysis Range
Deaths averted at six months	3.4	-
LYGs	58.5	29.4-87.9
dQALYs gained	21.3	2.7-33.5

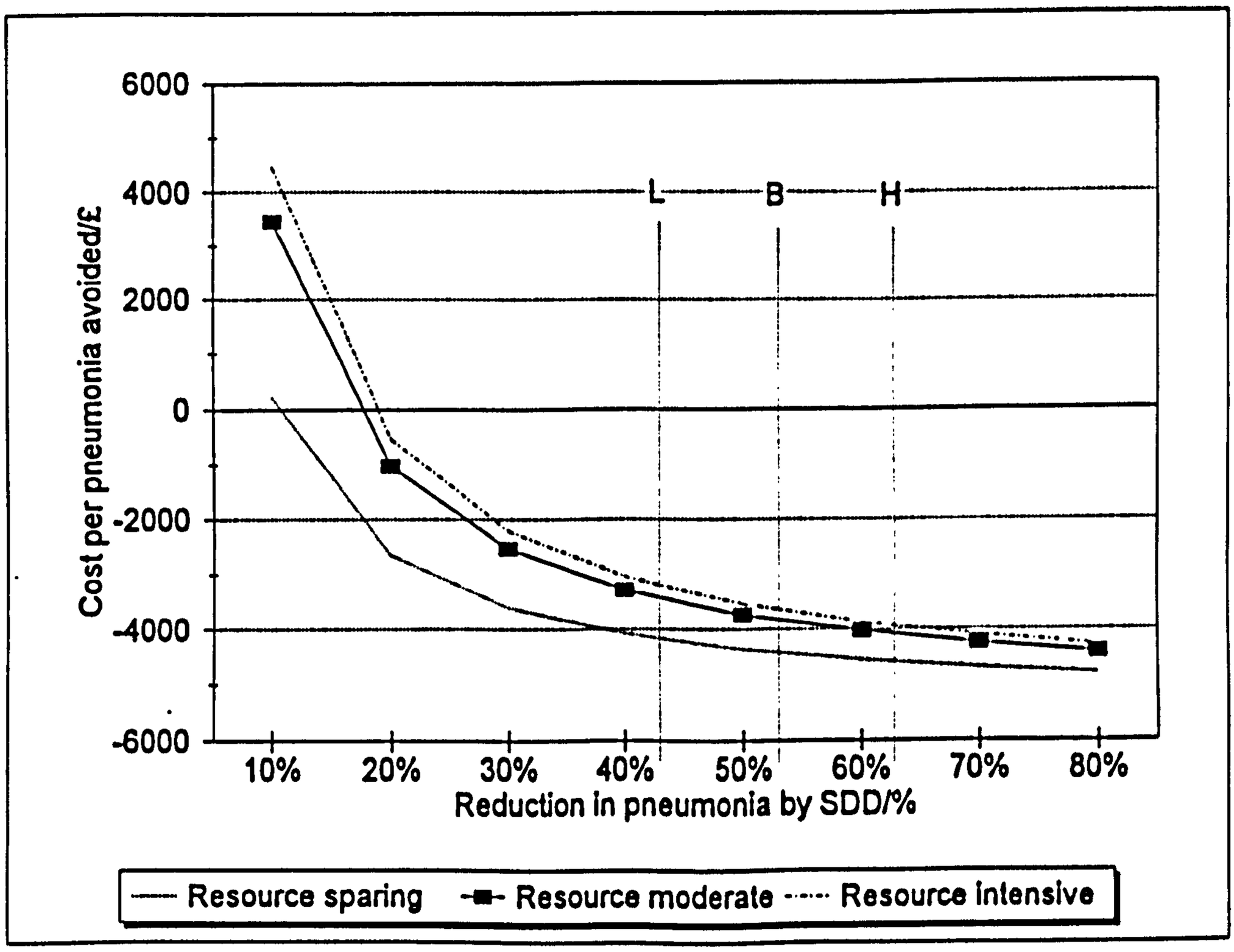
8.7.4 Effect of SDD Regimen

This section examines the impact of varying the components of the SDD regimen to make it more or less resource intensive. Table 8.12 summarises the effect of using the three regimens outlined in section 8.5.1. This is also depicted graphically in Figures 8.6a and 8.6b. This sensitivity analysis suggests that SDD is dominant at both centres however resource intensive the SDD regimen. Therefore, the conclusion that SDD is dominant at LTH and DGH is insensitive to the cost of the SDD regimen.

Table 8.12 Effect of Variation of SDD Regimen on Cost/Outcome Ratios at Both Centres

Effect of different SDD regimens on cost/outcome ratios	Incremental cost/£	
Cost per pneumonia avoided	DGH	LTH
Resource intensive SDD regimen	-1711	-3653
Resource moderate SDD regimen (base case)	-2109	-3832
Resource sparing SDD regimen	-3179	-4428
Incremental cost per six month survivor		
Resource intensive SDD regimen	-259	-1246
Resource moderate SDD regimen (base case)	-319	-1307
Resource sparing SDD regimen	-481	-1511

Figure 8.6a Effect of Different SDD Regimens on Incremental Cost per Pneumonia Avoided at LTH

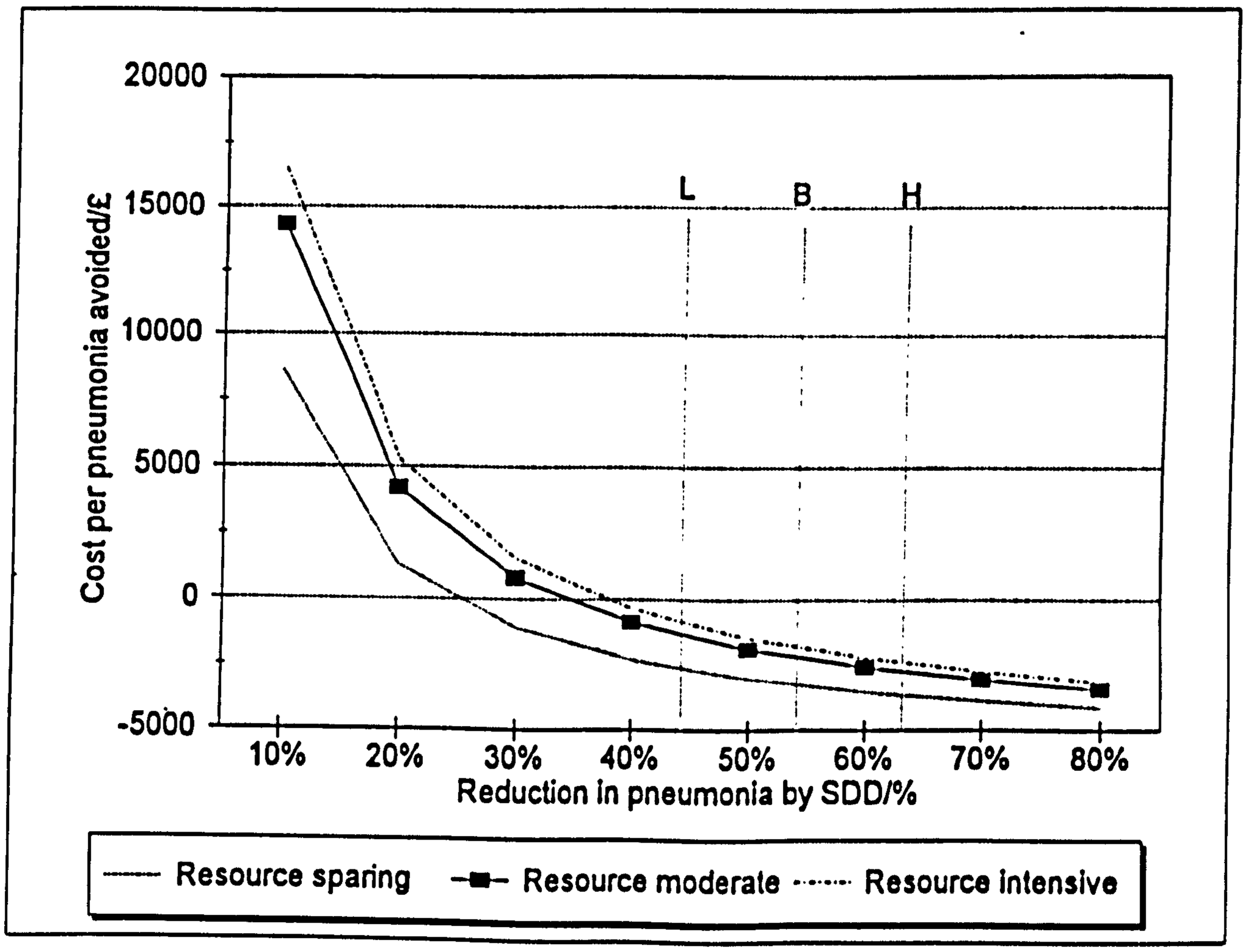


L: Low estimate for decrease in pneumonia rate (43%)

B: Base estimate for decrease in pneumonia rate (53%)

H: High estimate for decrease in pneumonia rate (63%)

Figure 8.6b Effect of Different SDD Regimens on Incremental Cost per Pneumonia Avoided at DGH



L: Low estimate for decrease in pneumonia rate (43%)

B: Base estimate for decrease in pneumonia rate (53%)

H: High estimate for decrease in pneumonia rate (63%)

8.7.5 Effect of Increase in Length of ICU Stay Attributable to Pneumonia

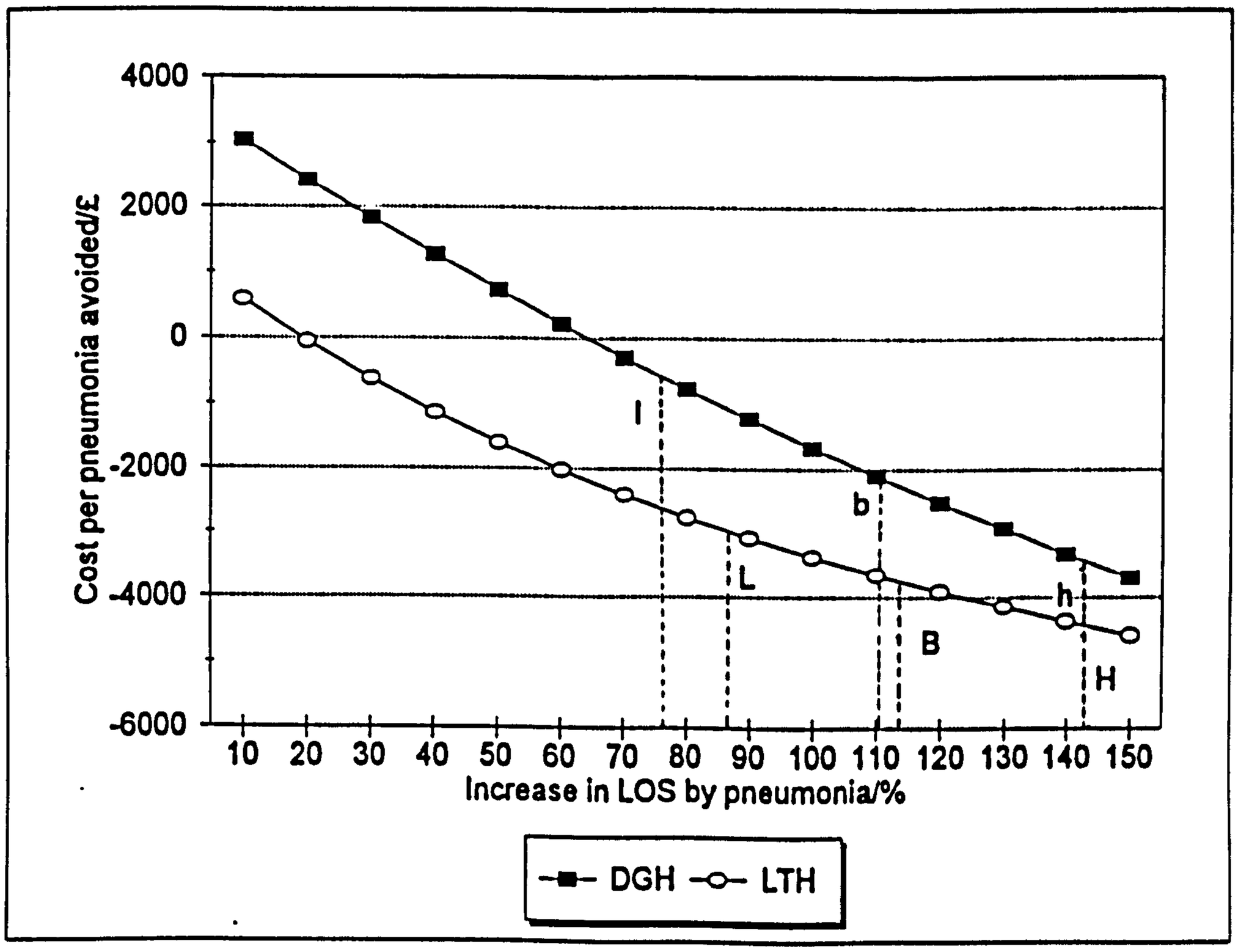
The base case model for DGH and LTH assumes an increase in length of ICU stay due to pneumonia of 111% and 116%, respectively. These values were derived from linear regression and have 95% confidence intervals associated with them. This section examines the effect on the conclusion that SDD is dominant at both centres if the increase in length of stay is varied up to these ranges for each centre. Table 8.13 summarises the effect of this variation on cost/outcome ratios. It can be seen that SDD becomes more cost effective as length of stay increase due to pneumonia is increased. This is illustrated in Figure 8.7, where the variation in cost per pneumonia avoided only is examined.

SDD becomes the dominant therapy if the increase in length of ICU stay due to pneumonia is at least 20% at LTH, and at least 65% at DGH. This sensitivity analysis suggests that SDD is dominant at both centres within the 95% confidence intervals of the increase in length of ICU stay attributable to ICU-acquired pneumonia. Therefore, the conclusion that SDD is dominant at LTH and DGH is insensitive to the variation in this parameter.

Table 8.13 Effect of Variation of Increase in Length of ICU Stay by Pneumonia at Both Centres

↑ Length of ICU stay by pneumonia	Cost per pneumonia avoided/£	Cost per six month survivor/£
DGH		
↑78% (Lower limit)	-758	-115
↑111% (Base value)	-2109	-319
↑144% (Upper limit)	-3501	-530
LTH		
↑88% (Lower limit)	-3081	-1051
↑116 (Base value)	-3832	-1307
↑144% (Upper limit)	-4467	-1524

Figure 8.7 Graph to Show Effect of Variation of Increase in Length of ICU Stay Due to Pneumonia at LTH and DGH



LTH:

L: Low estimate for increase in length of stay (88%)

B: Base estimate for increase in length of stay (116%)

H: High estimate for increase in length of stay (144%)

- *DGH:*

  l: Low estimate for increase in length of stay (78%)

  b: Base estimate for increase in length of stay (111%)

  h: High estimate for increase in length of stay (144%)

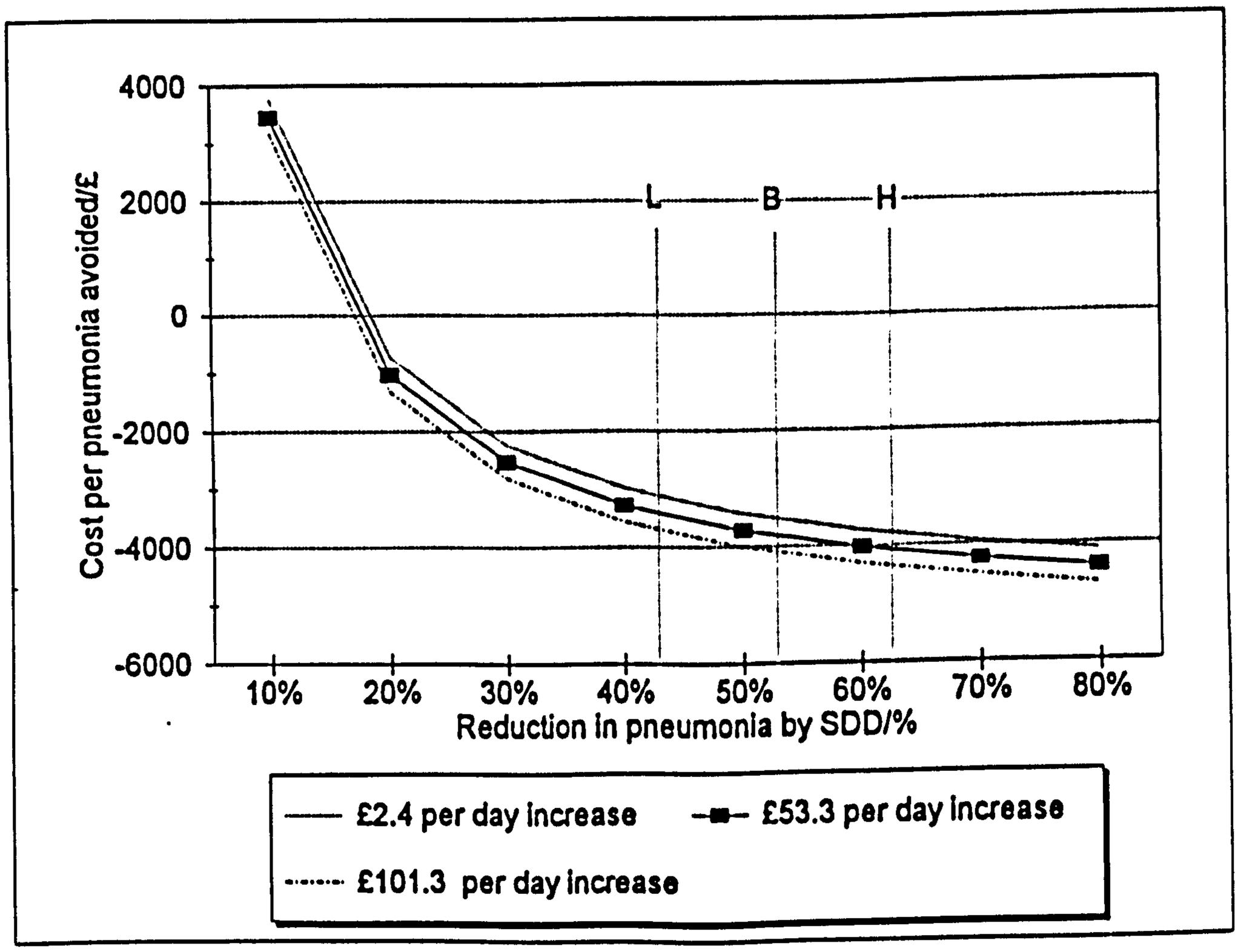
8.7.6 Effect of Increased Treatment Intensity

Increase in treatment intensity due to ICU-acquired pneumonia is only reported to occur at LTH. The increase in variable cost per patient day derived from the LTH dataset is £53.3 (95% CI: £2.4-£101.3). Table 8.14 summarises the effect of this variation on cost per pneumonia averted and cost per six month survivor. This sensitivity analysis suggests that SDD is dominant within the 95% confidence intervals of the increase in variable cost per patient day attributable to ICU-acquired pneumonia. Therefore, the conclusion that SDD is dominant at LTH is insensitive to the variation in this parameter. This is illustrated in Figure 8.8, where the variation in cost per pneumonia avoided only is examined.

Table 8.14 Effect of Variation of Increase in Variable Cost per Patient Day by ICU-Acquired Pneumonia at LTH

↑ Variable cost per patient day by pneumonia/£	Cost per pneumonia avoided/£	Cost per six month survivor/£
↑ £2.4 (Lower limit)	-3538	-1207
↑ £53.3 (Base value)	-3832	-1307
↑ £101.3 (Upper limit)	-4114	-1404

Figure 8.8 Graph to Show Effect of Variation of Variable Cost per Patient Day Due to Pneumonia at LTH



L: Low estimate for decrease in pneumonia rate (43%)

B: Base estimate for decrease in pneumonia rate (53%)

H: High estimate for decrease in pneumonia rate (63%)

8.7.7 Summary of Sensitivity Analysis

In summary, this sensitivity analysis has suggested that the conclusion that SDD is dominant at both centres is robust to variation in underlying parameters. The sensitivity analyses carried out are summarised below.

8.7.7.1 Increases in SDD effectiveness increase the cost effectiveness of SDD. The conclusion that SDD is dominant at both centres was not affected by variation in this parameter.

8.7.7.2 Increased base ICU-acquired pneumonia rates lead to increased cost effectiveness of SDD. The conclusion that SDD is dominant at LTH was not affected by variation in this parameter. At DGH, however, SDD lost dominance if this parameter was varied.

8.7.7.3 The assumption that there is an increase in short term mortality due to ICU-acquired pneumonia means that SDD could reduce mortality rates and increase LYGs and QALYs gained by ICU patients. Although there was much uncertainty around the estimates for LYGs and QALYs gained, this did not change the conclusion that SDD was dominant at both centres.

8.7.7.4 More resource intensive versions of the SDD regimen could reduce the cost effectiveness of SDD. However, the conclusion that SDD is dominant at both centres was not affected by variation in this parameter.

8.7.7.5 The larger the increase in length of ICU stay attributable to ICU-acquired pneumonia, the more cost effective SDD could become. However, the conclusion that SDD is dominant at both centres was not affected by variation in this parameter.

8.7.7.6 The more costly it is to treat a patient with pneumonia, the more cost effective SDD could become. However, the conclusion that SDD is dominant at LTH was not affected by variation in this parameter.

8.8 AN EXAMINATION OF THE 'ADDED VALUE' OF THE ECONOMIC EVALUATION OF SDD AT LTH AND DGH

This section compares the results obtained from this economic evaluation with those obtained from the economic evaluation of SDD in Chapter Four. Whether there is 'added value' gained from the addition of empirical evidence is examined. Added value can be interpreted as an increase in robustness or relevance of conclusions. This may be due to a decrease in an area of uncertainty, quantification of an area of uncertainty or use of clinical or economic evidence that is more relevant to a particular setting. The impact of clinical and economic evidence on the robustness of conclusions is investigated. Reasons for differences between the conclusions for the two centres are suggested.

8.8.1 Impact of Improved Clinical Evidence

The areas of clinical evidence required for economic evaluation of SDD are the effectiveness of SDD in reducing ICU-acquired pneumonia rates, base ICU-acquired pneumonia rates, and the impact of ICU-acquired pneumonia on long term mortality and morbidity. The impact of variation of these parameters on conclusions is examined in this section.

8.8.1.1 Effect of Information Regarding SDD Effectiveness

The ability of SDD to reduce ICU-acquired pneumonia rates has been shown by both economic evaluations in this thesis to have a very large impact on SDD's cost/outcome ratios. The large amount of clinical evidence available suggests that SDD has a relatively consistent effect on reducing ICU-acquired pneumonia rates, in a clinical trial context at least. A succession of meta-analyses have produced similar point estimates for reduction in pneumonia rates. The point estimate (53%) produced by the meta-analysis in Chapter Four has very narrow confidence intervals (43% to 63%) indicating that the point estimate is precise. Therefore, although variation in effectiveness affects cost/outcome ratios significantly, in practice, this variation is not expected to occur. However, these point estimates for effectiveness are actually point estimates for *efficacy* of SDD as measured within the conditions of an RCT. *Effectiveness* of SDD is the ability of SDD to reduce ICU-acquired pneumonia rates in a practice setting. Due to less rigorous patient selection and deviation from recommended practices and regimens, the effectiveness of SDD is likely to be lower than its efficacy. The two economic evaluations in this thesis use published efficacy data. This reliance on secondary clinical data reduces the relevance of the economic evaluations to the centres in which they are based.

8.8.1.2 Effect of Local Epidemiological Information on Pneumonia Rates

The economic evaluation in Chapter Four illustrated that variations in local ICU-acquired pneumonia incidence rates have a very large effect on the cost/outcome ratios of SDD. Knowing the local pneumonia rate therefore eradicates the possibility of this variation in the economic evaluation of SDD at LTH and DGH. The conclusion that SDD is

dominant is, therefore, more robust due to this extra information. The economic evaluation in Chapter Four suggested that the higher the local pneumonia rate, the more cost effective SDD is shown to be. This is illustrated in the economic evaluation reported in this chapter.

8.8.1.3 Effect of Information Regarding Impact of ICU-Acquired Pneumonia on Mortality and Morbidity

Chapter Four suggested that there was a lack of evidence available on the effect of SDD on the ultimate outcome of the patient, in terms of mortality and morbidity. It is probable that ICU-acquired pneumonia may increase mortality in the short term. This assumption is used in the economic evaluation in Chapter Four. Values were derived from the meta-analysis of SDD trials, so were secondary data, not measured on the actual patient group to which they were applied. This, and their algebraically derived nature, decreased the robustness of conclusions drawn when using them.

The statistical analysis reported in Chapter Six suggested that there was no increase in short term mortality that could be attributed to ICU-acquired pneumonia. It was suggested that the lack of effect detected was largely due to the insufficient patient group sizes. The impact of an increase in mortality due to ICU-acquired pneumonia as derived in Chapter Four was examined in the sensitivity analysis for this economic evaluation.

There is no published evidence on the impact of SDD or ICU-acquired pneumonia on longer term mortality or morbidity. The lack of evidence meant that alternative sources had to be used in the economic evaluation in Chapter Four. The resultant cost/outcome ratios were very tentative with very wide and arbitrary ranges. In the economic analysis

in this chapter, the same sources for long term mortality and morbidity were used as for the economic evaluation in Chapter Four. This variation did not affect conclusions about the cost effectiveness of SDD in any of the economic evaluations.

8.8.2 Impact of Improved Economic Evidence

The areas of economic evidence required for economic evaluation were resource use and associated unit costs arising from SDD implementation and the maintenance of ICU-acquired pneumonia. This latter category can be divided into increased length of ICU stay due to ICU-acquired pneumonia, cost associated with one patient day on ICU and increased cost associated with increased therapeutic intensity.

8.8.2.1 Effect of Information on SDD Regimen

In the secondary economic evaluation in Chapter Four, the most common SDD regimen reported in the SDD trials was used and local British costs were attached to it. The types of regimens reported were relatively uniform. The more resource sparing regimens examined were more cost effective. In the revised economic evaluation reported in this chapter, the SDD regimens used were based on a survey of SDD use in the UK. Costs from the two study centres were attached to these regimens. Again, the more resource sparing regimens provided SDD with the opportunity to be more cost effective, although the variation was not particularly large. However, the dominance of SDD was not affected by varying the regimen used.

In the economic evaluation in this chapter, use of SDD regimens known to be used in the UK and costs appropriate to that particular centre

increased the relevance of the costs of the SDD regimens. The dominance of SDD was not affected at either centre by varying the regimen used.

8.8.2.2 Impact of Information on Increase in ICU Length of Stay by ICU-Acquired Pneumonia

The economic evaluation in Chapter Four suggested that the extent of increase in ICU length of stay by ICU-acquired pneumonia had a significant impact on the cost effectiveness of SDD. The larger the increase, the more cost effective SDD became. The increase in length of ICU stay was algebraically derived from the meta-analysis of SDD trials. The conclusion that SDD was a dominant therapy was sensitive to variation in this parameter, due to the wide ranges employed for sensitivity analysis. The economic evaluation in this chapter used increases in length of ICU stay statistically derived from empirical data. The mean increases had associated 95% confidence intervals, so the uncertainty surrounding point estimates was quantified. Variation within these ranges did not affect the conclusion that SDD was dominant at either centre. The conclusion that SDD is dominant is, therefore, more robust due to this extra information.

8.8.2.3 Effect of Information on Cost per Patient Day

In the economic evaluation reported in Chapter Four, the cost per day on intensive care was derived from a British study and inflated to a current year, giving a value of £886 per day. The costs were rigorously collected in the study and were British, increasing their relevance. However, they were four years old, so this decreased their robustness. Using this data, increased cost per day was demonstrated to moderately

increase the cost effectiveness of SDD. Large variations in cost per day were necessary to reverse the conclusion that SDD was dominant. The economic evaluation reported in this chapter uses costs per ICU day that have been empirically determined. This is considered to increase the applicability and relevance of the economic evaluation to each centre.

8.8.2.4 Effect of Information on Costs Associated with Treatment of Pneumonia

The economic evaluation in Chapter Four examined the impact of an increase in treatment intensity associated with the treatment of pneumonia on cost/outcome ratios. Secondary evidence on this was very difficult to find. This meant that multiple sources had to be used, most of which were not British and not very current. The final estimates achieved were not very precise and wide sensitivity ranges had to be used. Sufficient variation in this parameter reversed the conclusion that SDD was dominant.

The empirical study reported in Chapters Six and Seven was able to identify an increase in variable cost per day (with 95% confidence intervals) at LTH, but not at DGH. Variation within these ranges did not affect the conclusion that SDD was dominant. The conclusion that SDD is dominant is, therefore, more robust due to this extra information.

8.9 REALISABLE COST SAVINGS FROM THE IMPLEMENTATION OF SDD

This section examines to what extent the theoretical cost/outcome ratios that have been derived in this economic analysis can be translated into realisable cost savings at either centre. Local organisational factors

that may affect realisable cost savings that are considered here are ICU occupancy rates and patient refusal rates. Each centre is considered separately.

8.9.1 Realisable Cost Savings at LTH

This economic evaluation has suggested that, given the conditions stated, the implementation of SDD at LTH reduces the incidence of ICU-acquired pneumonia, at a lower cost. The use of SDD in 171 ventilated patients, admitted over a period of 11 months, results in theoretical cost savings of £111131. This would be equivalent to treating 187 ventilated patients at a saving of £121234 per year.

In practice, local organisational factors will affect this theoretical cost saving. LTH ICU has a mean occupancy of 93.5% (range 88.4 to 97.7%) and a mean refusal rate of 44% (range 26 to 65%). Total admissions for 1994 were 259. This means that a further 220 admission requests were refused. This refusal rate does not take account of early ICU discharges and may include one patient being refused more than once. However, these figures suggest that this ICU is a high occupancy unit that turns away a significant proportion of potential admissions. The reasons for refusal were not recorded. According to Metcalfe *et al* [1995], 31% of ICU refused admissions in the UK in 1992 were appropriate, that is, the patient was not suitable for ICU. The remaining refused admissions were due to the size of the unit and lack of nursing staff. If this proportion is assumed to approximate to the situation at LTH, this would mean that of the 220 refused admissions, 68 were turned away appropriately and 152 were refused admission due to the ICU being full or not having enough staff.

The use of SDD reduces the length of stay of 29 ventilated patients who do not contract late-onset Gram-negative pneumonia from 8.9 to 4.1 days. In the 171 patients studied, this equated to 139 patient days being made available by SDD. In one year this would make available 152 patient days, equivalent to 0.41 ICU beds. If occupancy of these beds is 93.5%, this suggests that 142.1 patient days could be otherwise utilised. These could, in theory, be filled by erstwhile refused admissions. The mean length of ICU stay of ICU patients at LTH in general is 6.83 days. This suggests, therefore, that an extra 21 patients could be treated on the ICU if SDD were implemented. This would increase annual admissions to 280 and reduce the mean patient refusal rate to 41.5%.

This increase in patient turnover at a constant level of occupancy will affect the resource use of the ICU, as described in Chapter Four. If the patient days made available by SDD are immediately filled, as suggested above, the occupancy of the unit is not decreased. So, the ICU is required to run at the same occupancy level as before. Fixed costs cannot be 'saved' in practice, as they are independent of activity. Nursing costs are also not 'saved' in practice, as they will be directed to the extra admissions. Variable costs saved by the shorter length of ICU stay will also not be saved in practice as they will be absorbed by the extra admissions. Also, there would be the added cost of SDD implementation. This would equate to £53519 per year to treat 187 ventilated admissions. Therefore, the introduction of SDD could theoretically increase the patient turnover of the ICU by 21 patients per year at an added cost of £53519.

However, from the perspective of the refused admissions, the opportunity cost associated with refusal would be avoided. Metcalfe *et al* [1995] did not find an increase in hospital mortality among refused admissions, that could be attributed to their refusal. There is no

evidence available on the impact of refusal on long term mortality or morbidity. Reduction in the refusal rate reduces costs to the hospital of having to find another ICU bed at another hospital for that patient, the costs of transporting that patient, and the costs to the second choice ICU of caring for that patient. If these costs were quantified and taken into account, the cost savings from SDD implementation could be significantly larger.

8.9.2 Realisable Cost Savings at DGH

An equivalent consideration of realisable cost savings was made at DGH. This economic evaluation has suggested that, given the conditions stated, the implementation of SDD at DGH reduces the incidence of ICU-acquired pneumonia, at a lower cost. The use of SDD in 89 ventilated patients, admitted over a period of 11 months, results in theoretical cost savings of £16915. This would be equivalent to treating ventilated 97 patients at a saving of £18453 per year.

Again, local organisational factors will affect this theoretical cost saving. DGH ICU had an occupancy of 67.2% in 1994 (range not reported). The refusal rate of was not known. Total admissions for 1994 were 206. On the basis of this low occupancy, it is assumed, for this exercise, that any refusals would have been due to the inappropriateness of the patients, rather than because the ICU was full.

The use of SDD reduces the length of stay of eight ventilated patients who do not contract late-onset Gram-negative pneumonia from 10.9 to 5.2 days. In the 89 patients studied, this equated to 45.6 patient days being made available by SDD. In one year this would make available 49.7 patient days, equivalent to 0.14 ICU beds. However, as the ICU is

underutilised at the moment, it is unlikely that these patient days will be taken up by other patients. The occupancy of the unit could theoretically decrease from 67.2% to 63.8%.

This decrease in occupancy at a constant patient turnover would affect costs. Fixed costs are not affected by occupancy. Therefore, in reality, these costs (£9075 per year) are not saved. Medical and nursing costs may not be partly saved in reality. In the event of low occupancy, nurses and medical staff are deployed to work on other wards. If all staff were redeployed, the cost of employing them is still incurred (£22683). The variable costs associated with these unused patient days would be saved because there would an actual reduction in resource use. This would lead to a saving of £15268. However, it would cost £28580 to implement SDD and treat the 97 ventilated patients with it. Therefore, the cost savings would have to take this into account. So in reality, the variable costs would be saved and the SDD costs, staff and fixed costs would still be incurred. This would result in an annual *increase* in cost of £13305.

8.10 CONCLUSIONS AND IMPLICATIONS FOR POLICY

The aim of the economic evaluation reported in this chapter was to assess whether SDD could be shown to be cost effective if it were implemented at two British ICUs. One was located in a London teaching hospital and the other in a district general hospital. The secondary economic evaluation reported in Chapter Four had recommended that improved economic and patient outcome evidence was required. This chapter has described an economic evaluation of SDD applying primary economic evidence to the decision-analytic model developed in Chapter Four.

Section 8.4 described the clinical evidence required for this economic evaluation. The SDD efficacy and long term mortality and morbidity evidence used in Chapter Four was also used here. Base pneumonia rates and six month mortalities were obtained from the study in Chapter Six. Section 8.5 described the economic evidence required. Details on SDD regimens were obtained from a survey (Chapter Five). Evidence on increase in length of ICU stay due to ICU-acquired pneumonia, costs per ICU day and costs associated with treating an episode of pneumonia were obtained from the study in Chapter Six. The incremental economic analysis concluded that SDD improved patient outcomes at a lower cost, so was dominant, at both centres (section 8.6). The sensitivity analysis in Section 8.7 examined the robustness of this dominance to the various clinical and economic parameters used. The conclusion that SDD was dominant was robust to variation of underlying parameters.

Section 8.8 went on to compare this economic evaluation with the secondary economic evaluation reported in Chapter Four. Whether the use of primary economic evidence fulfilled its objective in improving the robustness of conclusions was examined. Improved information was available on resource use and unit costs of the SDD regimen; local pneumonia incidence rates; increased length of ICU stay due to pneumonia; cost per ICU day; and costs associated with treating pneumonia. It was concluded that this improved evidence decreased uncertainty around parameters. This reduced the levels of variation in the sensitivity analysis, such that the conclusion that SDD was a dominant therapy was made even more robust than it was in Chapter Four.

The lack of information on the impact of SDD, ICU-acquired pneumonia, or admission to ICU in general, had on long term morbidity and mortality continued to severely restrict the conclusions that could be made about the impact of SDD on ultimate patient outcomes.

Section 8.9 assessed to what extent the theoretical cost savings that had been derived in this economic evaluation could be translated into realisable cost savings at either centre. Patient occupancy rates at the two centres were shown to significantly affect realisable cost savings. It was suggested that there may actually be an *increased* cost to the ICU if SDD were implemented at LTH or DGH.

This economic evaluation has provided evidence on the theoretical cost effectiveness of SDD if it were to be implemented at these two centres. It has suggested that SDD can be shown to be dominant in two types of British ICU. The conclusions made at LTH and DGH could possibly be generalised to other British teaching hospitals and district general hospitals. The decision-analytic model developed was applied successfully to both centres, so it is reasonable to assume that it would also work in other centres. The published effectiveness data on SDD would have the same level of relevance as it does for these two centres. The generalisability of the study to other centres is higher than that of the secondary economic evaluation in Chapter Four because of the use of current economic data from local practice settings. The conclusions have been shown to be very robust, even in the face of substantial variation of underlying parameters. This implies that the conclusion that SDD is dominant could be applied to other ICUs.

Policy-makers considering implementing SDD have three options. The first option is to directly apply the evidence from this economic evaluation to their own setting, undertaking no extra work. This could occur if the policy-makers believed that the economic, epidemiologic and clinical evidence were sufficiently generalisable to their setting. The second option is to substitute local pneumonia rates, resource use and costs into the decision-analytic pathway developed by this thesis. This would occur if decision-makers were happy with the effectiveness data,

but felt that local economic and epidemiologic data were needed to derive conclusions about SDD that were applicable to their setting.

The third option would be that used by decision-makers who do not believe that the published efficacy evidence on SDD is applicable to their situation. In this situation, it would be necessary to set up a study of SDD in their ICU to measure its *effectiveness* and cost implications in their practice setting.

In conclusion, the recommendation from this economic evaluation is that SDD implementation on ICUs should be considered again by policy-makers, in light of this new evidence.

Chapter 9: Conclusions and Recommendations for Future Research

The primary objective of this thesis was to examine whether SDD could be demonstrated to be cost effective, using modelling in economic evaluation as an alternative to RCT-linked studies. The secondary objective was to examine whether modelling in economic evaluation could generally be used in evaluating intensive care interventions, as a realistic alternative to RCT-linked evaluations.

The need for economic evaluation in intensive care and its constituent technologies was suggested in Chapter Two. Through a consideration of published evidence, the significant economic impact of intensive care on the health care systems of industrialised countries was illustrated. The annual spending on intensive care in the US was shown to be twenty times higher *per capita* than that in the UK. It was considered that the structure of the health care system in general is likely to contribute partly to this difference. However, it also reflects the lack of consensus about the optimal use of intensive care. Decisions on appropriate use of intensive care and its specific therapies are prevented by the lack of information available on allocative or technical efficiency of intensive care.

This review suggested that intensive care medicine is unable to accurately account for its resource use or measure its impact on health outcomes. Reasons for the lack of research into the technical efficiency of intensive care and its constituent technologies were discussed. The absence of evidence for effectiveness of technologies used in intensive care was attributed particularly to the difficulties associated with carrying out RCTs in the intensive care environment. Additionally, little research has been carried out the effects of intensive care on mortality and morbidity, so the long term impact of intensive care is not known.

The economic impact of intensive care and its technologies is also not known due to the lack of rigorously carried out economic research in this area. This review concluded that economic evaluation of technologies used in intensive care is needed, but that alternative methods of economic evaluation incorporating modelling need to be further developed and tested, rather than relying on the attachment of economic evaluation to RCTs, with all their problems.

Chapter Three introduced the specific clinical area investigated by this thesis. ICU-acquired pneumonia, an iatrogenic event, was shown to have potentially major clinical and economic implications. SDD is a resource intensive intervention, used on ICU to prevent ICU-acquired pneumonia. Thirty-seven RCTs of SDD have been published, none with a formal economic evaluation. Also, no long term outcomes have been investigated. It was suggested that further investigation into the economic and long term clinical impact of SDD was required. This review concluded that a formal assessment of costs and benefits was required to inform the debate on the cost effectiveness of SDD.

Chapters Two and Three suggested that alternative methods of economic evaluation were necessary if the economic evaluation of technologies in intensive care in general and SDD in particular was to be taken forward. Chapter Four, therefore, described a secondary economic evaluation of SDD, combining modelling techniques with published clinical and economic evidence. The research question was defined in terms of a decision-analytic model.

Application of published evidence to this model uncovered significant limitations to the clinical and economic data available. Although there was a large quantity of stochastic clinical evidence, it was not always presented in such a way as to be of use in the decision-analytic model. Also, only intermediate outcome measures were used in SDD trials to

assess the clinical effectiveness of SDD. It also showed that the little economic evidence available was deterministic, old and from a range of non-UK practice settings. The weakness of much of the evidence was reflected by the wide ranges recommended for the sensitivity analysis.

The incremental economic analysis of SDD suggested that SDD was a dominant therapy. The subsequent sensitivity analysis showed that this conclusion was robust through substantial variation of the underlying clinical and economic parameters. The parameters that reversed the conclusion that SDD was dominant, when varied sufficiently, were effectiveness of SDD, base pneumonia rates, increase in length of ICU stay by pneumonia, cost per ICU day and costs associated with treating pneumonia. Variations in base pneumonia rate and the economic cost of an episode of pneumonia reduced the robustness of the conclusions because the degree of uncertainty around them was not known. It was concluded from this analysis that improved evidence on long term outcomes of patients and the economic impact of ICU-acquired pneumonia and SDD was needed to better inform conclusions on cost effectiveness. This thesis concentrated on improving the economic evidence on the impact of ICU-acquired pneumonia and SDD. Investigation into the long term mortality and morbidity of ICU patients is urgently required, but could not be investigated within the timescale of this thesis.

A national postal survey was undertaken to provide detailed information about the state of SDD implementation in Britain (Chapter Five). This survey had a high response rate and showed that SDD was not widely used in this country, only 5% of ICUs reporting that they used it. This contrasted with the high profile that it has in the medical literature. Its use was also shown to be declining. There were two main reasons given by ICU clinicians for not using SDD. The first reason was that they considered it was too expensive. The second reason was that they

did not believe that it decreased mortality. This survey provided information on the resource use and unit costs associated with SDD regimens used around the country.

An observational study was carried out at two typical British ICUs to obtain primary economic data on the impact of ICU-acquired pneumonia. The study also obtained epidemiologic data on the incidence of ICU-acquired pneumonias. Patient-specific (bottom-up) resource use data was obtained. Local unit costs for that resource use were obtained using rigorous methods. This provided individual patient costs, allowing interpatient variation to be investigated. The advantages of this evidence over that available prior to this study are that it is the first British evidence on the impact of ICU-acquired pneumonia on patient cost.

Two operational issues were highlighted by this study. The first concerned the retrieval of data. It was necessary to access multiple sources of data on a regular basis, which made the study labour intensive. This suggested that this type of study, whilst providing detailed data, could not be carried out on a routine basis until hospital recording systems are better integrated. The lack of computerised records at DGH, in particular, significantly compromised the quality of resource use data that could be obtained.

The data from this study were used to determine the impact of ICU-acquired pneumonia on economic parameters (Chapter Seven). This was carried out using multiple regression analysis, to control for factors other than ICU-acquired pneumonia that can affect cost. These other factors included the use of haemodialysis and the insertion of pulmonary artery catheters. This analysis suggested that ICU-acquired pneumonia increased ICU length of stay at both centres. An increase in treatment intensity was also detected at LTH.

The economic evidence obtained from Chapters Five to Seven was used in an economic evaluation of SDD at each ICU, reported in Chapter Eight. The epidemiologic and economic data for each centre was incorporated into the decision-analytic model developed in Chapter Four. The theoretical economic impact of SDD, if it were implemented at the two ICUs, was investigated. This analysis suggested that both centres would theoretically have improved outcomes at lower costs, that is, SDD was shown to be the dominant therapy at both ICUs.

The subsequent sensitivity analyses showed that these conclusions were robust through variation of the underlying clinical and economic parameters. ICU-specific information on base pneumonia rates and patient costs meant that these parameters were associated with much less uncertainty. The robustness of the conclusion that SDD is a dominant therapy varied between the two centres. For example, SDD remained dominant at LTH at much lower levels of effectiveness than at DGH. This was explained by the higher pneumonia incidence at LTH. In this analysis, the uncertainty around the LYGs and dQALYs gained, as defined by this thesis, did not affect the robustness of the conclusion that SDD was dominant. However, until further evidence on the long term impact of intensive care is available, cost/LYG and cost/QALY ratios for SDD can only be very tentative.

So, the economic evaluation described in Chapter Eight has suggested that SDD is a dominant therapy across a wide range of clinical, epidemiologic and economic conditions. However, according the survey described in Chapter Five, the large majority of ICU clinicians in the UK do not use SDD. The two main reasons are that they do not believe that it has any effect on mortality and that it is too expensive. The economic evaluations of SDD reported in this thesis do not add new evidence to the debate on mortality reduction by SDD, although examination of published evidence suggests there is a link. However,

these economic evaluations have illustrated that although SDD has cost implications of its own, the reduction in incidence of ICU-acquired pneumonia results in a reduction in overall cost. The recommendation from this economic evaluation is that SDD implementation on ICUs should be considered again by policy-makers, in light of this new evidence.

The conclusions from this economic evaluation have implications for future policies concerning the implementation of SDD in particular, and, more generally, implications for the use of modelling in economic evaluation. In policy terms, a therapy that has been demonstrated to be so generally dominant should be recommended for implementation. As discussed in Chapter Eight, policy-makers considering the implementation of SDD on their ICU have three options on how they use the evidence presented in this thesis. Firstly, they could directly apply the evidence to their local setting. Secondly, they could substitute local epidemiologic and economic evidence into the decision-analytic model. The third option is to implement SDD in their ICU, and carry out a study on patient outcome, with an associated economic evaluation. Each of these three options has successively larger resource use implications.

To improve upon the economic evaluation reported in Chapter Eight, it would be necessary to implement SDD at the two centres to explore the real impact of SDD. The advantages of this would be the ability to measure SDD's effectiveness in a practice setting, rather than rely on published efficacy data. The actual local costs of implementing SDD could also be determined. However, the ideal economic evaluation is not necessarily one linked to an RCT. This does not reflect a normal practice setting so the resource use does not reflect practice either. Economic evaluations should ideally be carried out in more naturalistic settings to reflect normal practice more closely, with some degree of randomisation to allow comparison. Also, the cost effectiveness of SDD

should be considered in the context of other infection control methods in intensive care. Finally, the local organisational context needs to be considered, as shown by this thesis.

More generally, this thesis has illustrated how modelling can be used successfully in economic evaluation in intensive care. Modelling in economic evaluation has three purposes.

Firstly, it can be used as a preliminary exercise to assess whether prospective economic evaluation is warranted in a specific area. There are many areas that could be investigated and economic evaluation has resource use implications of its own, so priorities for research need to be identified.

The second situation where modelling can be used is when an economic evaluation attached to an RCT powered to detect economic differences is considered 'infeasible or unethical', a use recommended by the Standing Group on Health Technology [1994]. This thesis has highlighted many reasons why RCT-linked economic evaluations are not widely used in intensive care. Therefore, the way forward for the assessment of many technologies is through the use of modelling techniques like those described in this thesis. It is essential, therefore, that standard methods are developed so that confidence can be placed in the conclusions drawn from them.

The third use for modelling techniques in economic evaluation is to make an existing economic evaluation more relevant to a specific setting. This is done by substituting local clinical, economic or organisational evidence into an evaluation. The usefulness of this is demonstrated by this thesis. The difference between the theoretical economic impact and that which would be realised in practice needs to be examined in the context of the effect of local clinical, economic and

organisational factors. This type of modelling will always be necessary in some form as it would be undesirable for RCT-linked economic evaluations to be carried out locally for all interventions.

New technologies should only be introduced into ICU practice once their cost and benefit has been evaluated. The use of modelling techniques, in conjunction with good quality clinical and economic evidence, has been shown to enable derivation of robust conclusions. Of course, whether SDD is implemented is dependent upon factors other than cost effectiveness. However, cost effectiveness is a major component of a policy decision-making process. This thesis has contributed evidence that suggests SDD is cost effective, which can only better inform the decision-making process.

In conclusion, further research into the technical and allocative efficiency of intensive care is urgently required to identify which intensive care interventions are cost effective in which groups of patients. Wider social debate is required to address what levels of ICU provision can be considered optimal, or supportable. It is suggested by this thesis that the modelling techniques used here can allow economic evaluation to make a valuable contribution to that debate.

REFERENCES

Aaron H J. Serious and unstable condition. Financing America's health care. Washington: The Brookings Institution; 1991.

Advisory Group on Health Technology Assessment (National Health Service Management Executive). Assessing the Effects of Health Technologies. London: Department of Health; 1991.

Aerdts S J A. Prevention of lower respiratory tract infection in mechanically ventilated patients [Thesis]. Nijmegen, Holland: Nijmegen University Hospital; 1989.

Aerdts S J A; Clasner H A L; Van Dalen R; Van Lier H J J *et al.* Prevention of bacterial colonisation of the respiratory tract and stomach of mechanically ventilated patients by a novel regimen of selective decontamination in combination with initial systemic cefotaxime. Journal of Antimicrobial Chemotherapy. 1990; 26(Suppl A): 59-76.

Atkinson S W; Bihari D J. Selective decontamination of the gut. British Medical Journal. 1993; 306(286-287).

Ayres S M (Panel chairman). Consensus Conference-Critical Care Medicine. Journal of the American Medical Association. 1983; 250(6): 798-804.

Bams J L; Miranda D R. Outcome and Costs of Intensive Care. Intensive Care Medicine. 1985; 11: 234-41.

Barriere S L. The economic impact of HA-1A (Centoxin) against endotoxin. Pharmacoeconomics. 1992; 2: 408-413.

Bekes C; Fleming S; Scott E. Reimbursement for intensive care services under diagnosis-related groups. Critical Care Medicine. 1988; 16: 478-481.

Blair P; Rowlands B J; Lowry K; Webb H; Armstrong P. Selective decontamination of the digestive tract: a stratified, randomised, prospective study in a mixed intensive care unit. Surgery. 1991; 110: 303-310.

Boom S J; Ramsay G. Selective decontamination of the digestive tract in intensive care. Epidemiology of Infection. 1992; 109: 337-347.

Bootman J L; Townsend R J; McGhan W F. Principles of Pharmacoeconomics. Cincinnati: Harvey Whitney Books Company; 1991.

Borlase B C; Baxter J T; Benotti P N; Stone M; Wood E. Surgical intensive care unit resource use in a speciality referral hospital: I. Predictors of early death and cost implications. Surgery. 1991; 109: 687-693.

Briggs A; Sculpher M; Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. Health Economics. 1994; 3: 95-104.

British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary, 28th Edition. London: Pharmaceutical Press; 1994 Sep.

Brun-Buisson C; Legrand P; Rauss A; Richard C *et al*. Intestinal decontamination for control of nosocomial multiresistant gram- negative bacilli. Annals of Internal Medicine. 1989; 110: 873- 881.

Buxton M; Acheson R; Caine N; Gibson S. Costs and benefits of the heart transplant programmes at Harefield and Papworth Hospitals. London: Department of Health and Social Security; 1985.

Buxton M J; Dubois D J; Turner R R; Sculpher M J; Robinson P A; Searcy C. Cost implications of alternative treatments for AIDS patients with cryptococcal meningitis. Comparison of fluconazole and amphotericin B-based therapies. Journal of Infection. 1991; 23: 17-31.

Buxton M J. Are we satisfied with QALY's? What are the conceptual and empirical uncertainties and what must we do to make them more generally useful? Measures of the quality of life and the uses to which such measures may be put. Hopkins A ed.; London: Royal College of Physicians; 1992.

Central Statistics Office. CSO Annual Abstract Life Tables: United Kingdom 1986-1988. London: OPCS; 1991.

Cerra F B; Maddaus M A; Dunn D L; Wells C L *et al.* Selective decontamination reduces nosocomial infections but not mortality or organ failure in surgical intensive care patients. Archives of Surgery. 1992; 127: 163-169.

Chalfin D B; Holbein M E; Fein A M; Carlon G C. Cost-effectiveness of monoclonal antibodies to gram-negative endotoxin in the treatment of gram-negative sepsis in ICU patients. Journal of the American Medical Association. 1993; 269: 249-254.

Chang R W S; Jacobs S; Lee B. Predicting outcome among intensive care unit patients using computerized trend analysis of daily APACHE II scores corrected for organ system failure. Intensive Care Medicine. 1988; 14: 558-566.

Chelluri L; Pinsky M R; Grenvik A N A. Outcome of intensive care of the 'oldest-old' critically ill patients. Critical Care Medicine. 1992; 20(6): 757-761.

Civetta J M; Hudson-Civetta J A; Nelson L D. Evaluation of APACHE II for cost containment and quality assurance. Annals of Surgery. 1990; 212: 266-276.

Cockerill F R; Muller S R; Anhalt J P; Marsh M *et al.* Prevention of infection in critically ill patients by selective decontamination of the digestive tract. Annals of Internal Medicine. 1992; 117(7): 545-553.

Coello R; Glenister H; Fereres J *et al.* The cost of infection in surgical patients: a case control study, Journal of Hospital Infection. 1993; 25 p239-250.

Cohen I L; Lambrinos J; Fein A. Mechanical ventilation for the elderly patient in intensive care. Journal of the American Medical Association. 1993; 269(8): 1025-1029.

Colton T. Statistics in Medicine. Boston: Little, Brown and Company; 1974.

Coyle D; Tolley K *et al.* Discounting of health benefits in the pharmacoceconomic analysis of drug therapies. An issue for debate? Pharmacoeconomics. 1992; 2: 153-162.

Craig C P; Connelly S. Effect of intensive care unit nosocomial pneumonia on duration of stay and mortality. American Journal of Infection Control. 1984; 12: 233-238.

Craven D E; Kunches L M; Kilinsky V *et al.* Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation, American Review of Respiratory Diseases. 1986; 133: 792-796.

Craven D E; Steger K A; Barat L M *et al.* Nosocomial pneumonia: epidemiology and infection control, Intensive Care Medicine. 1992: 18; S3-S9.

Crew A D; Stoodley D C; Old S; Unsworth G D *et al.* A sampling study of bedside nursing activity in a cardiac surgical intensive care unit. Intensive Care Medicine. 1987; 13: 119-125.

Cullen D J; Civetta J M; Briggs B A; Ferrara L C. Therapeutic intervention scoring system: a method for quantitative comparison of patient care. Critical Care Medicine. 1974; 2: 57-60.

Cullen D J; Ferrara L C; Briggs B A; Walker P F *et al.* Survival, hospitalization charges and follow-up results in critically ill patients. New England Journal of Medicine. 1976; 294: 982-987.

Cullen D J. Results, charges and benefits of intensive care for critically ill patients. Update 1983. Critical Care Medicine. 1984; 12: 102-106.

Daschner F. Nosocomial infections in intensive care units. Intensive Care Medicine. 1985: 11; 284-287.

Davey P; Hernanz C; Lynch W *et al.* Human and non- financial costs of hospital-acquired infections, Journal of Hospital Infection. 1991: 18; 79-84.

Davis H; Lefrak S S; Miller D; Malt S. Prolonged mechanically assisted ventilation. Journal of the American Medical Association. 1980; 243: 43-45.

De Champs C L; Guelon D P; Garnier R M; Poupart M C *et al.* Selective digestive decontamination by erythromycin-base in a polyvalent intensive care unit. Intensive Care Medicine. 1993; 19: 191-196.

De Clerq H; de Decker Gh; Alexander J P; Huyghens L. Cost Evaluation of infections in intensive care. Acta Anaesthesiologica Belgica. 1983; 3: 179-189.

De Pew C L; Moseley M J; Clark E G; Morales C C. Open vs Closed system endotracheal suctioning: a cost comparison. Critical Care Nurse. 1994; February: 94-100.

Detsky A S; Stricker S C; Mulley A G; Thibault G E. Prognosis, survival and expenditure of hospital resources for intensive care. New England Journal of Medicine. 1981; 305: 667- 672.

DHSS (1988) Guidance on the control of infection in hospitals prepared by the joint DHSS/PHLS Hospital Infection Working Group, London: DHSS.

Dick W; Pehl S; Tzanova I; Heinrich W *et al.* Physician and nursing (personnel) requirements for ICU's. Clinical Intensive Care. 1992; 3: 116-121.

The Directory of Emergency and Special Care Units (1993), CMA Medical Data Ltd, Cambridge.

Dragsted L; Qvist J. Outcome from intensive care. A 5-year study of 1308 patients: methodology and patient population. European Journal of Anaesthesia. 1989; 6: 23-37.

Drummond M F; Stoddart G L; Torrance G W. Methods for the economic evaluation of health care programmes. Oxford: Oxford Medical Publications; 1987.

Drummond M F; Davies L. Economic analysis alongside clinical trials. International Journal of Technology Assessment in Health Care. 1991; 7: 561-573.

Eddy D M. A manual for assessing health practices and designing practice policies: the explicit approach. Philadelphia: American College of Physicians; 1992.

Evans R G. Strained mercy. The economics of Canadian health care. Toronto: Butterworths; 1984.

Fagon J-Y; Chastre J; Hance AJ *et al.* Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay, The American Journal of Medicine. 1993: 94; 281-288.

Fedullo T J; Swinburne A J. Relationship of patient age to cost and survival in a medical ICU. Critical Care Medicine. 1983; 11: 155-159.

Feeny D H; Torrance G W. Incorporating utility-based quality-of- life assessment measures in clinical trials. Medical Care. 1989; 27(Suppl): s190-s204.

Feldstein M. Hospital costs and health insurance. Cambridge: Harvard University Press; 1981.

Feldstein P J. Health Care Economics. New York: Wiley Medical Publications; 1979.

Ferrer M; Torres A; Gonzalez J; Puig de la Bellacasa J. Utility of selective digestive decontamination in mechanically ventilated patients. Annals of Internal Medicine. 1994; 120: 389- 395.

Flaherty J; Nathan C; Kabins S A; Weinstein R A. Pilot trial of selective decontamination for prevention of bacterial infection in an intensive care unit. The Journal of Infectious Diseases. 1990; 162: 1393-1397.

Fox M A; Peterson S; Fabri B M; Van Saene H K F *et al.* Selective Decontamination of the digestive tract in cardiac surgical patients. Critical Care Medicine. 1991; 19: 1486-1490.

Friedman L S. Microeconomic policy analysis. Berkeley: McGraw-Hill; 1984.

Gafni A (Centre for Health Economics and Policy Analysis, McMaster University). The standard gamble method: what is being measured and how it is interpreted. Ontario: CHEPA; 1991. (Paper 91-4).

Gastinne H; Wolff M; Dealatour F; Faurisson F *et al.* A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. New England Journal of Medicine. 1992; 326: 594-9.

Gaussorgues Ph; Salord F; Sirodot M; Tigaud S. Efficacite de la decontamination digestive sur la survenue des bacteriemies nosocomiales chez les patients sous ventilation mecanique et recevant des betamimetiques. Reanimation Soins Intensive Medicine Urgente. 1991; 7: 169-174.

George D L. Epidemiology of nosocomial ventilator-associated pneumonia. Infection Control and Hospital Epidemiology. 1993; 14: 163-169.

Gilbertson A A; Smith J M; Mostafa S M. The cost of an intensive care unit: a prospective study. Intensive Care Medicine. 1991; 17: 204-208.

Girotti M J; Brown S J. Reducing the costs of ICU admission in Canada without diagnosis-related or case-mix groupings. Canadian Anaesthetists' Society Journal. 1986; 33: 765-772.

Godard J; Guillaume C; Reverdy M-E; Bachmann P *et al.* Intestinal decontamination in a polyvalent ICU. Intensive Care Medicine. 1990; 16: 307-311.

Gow G; Buckley P. Selective decontamination of the digestive tract in a general intensive care population. Pharmaceutical Journal. 1993; 251(6763): r17.

Gross P A; Neu F C; Aswapokee P *et al.* Deaths from nosocomial infections: experience in a university hospital and a community hospital, American Journal of Medicine. 1980: 68; 219-223.

Gujarati D N. Basic Econometrics. New York: McGraw-Hill; 1988.

Gyldmark M. The relationship between resource use, outcome and patient characteristics in an intensive care unit. Presented to Health Economics Study Group Meeting. 1993; July: Unpublished.

Haley R W; Schaberg D R; Von Allmen S D *et al.* Estimating the extra charges and prolongation of hospitalization due to nosocomial infections: a comparison of methods, Journal of Infectious Diseases. 1980: 141; 248-257.

Haley R W; Culver D H; White J W; Morgan W M *et al.* The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. American Journal of Epidemiology. 1985; 121: 182-205.

Haley R W. Managing hospital infection control for cost- effectiveness, Chicago, USA: American Hospital Publishing Inc; 1986.

Ham C. Health policy in Britain. 3rd edition. London: MacMillan; 1992.

Hammond J M J; Potgieter P D; Saunders G L; Forder A A. Double blind study of selective decontamination of the digestive tract in intensive care. Lancet. 1992; 340: 5-9.

Hartenauer U; Thulig B; Diemer W; Lawin P. Effect of selective flora suppression on colonization, infection, and mortality in critically ill patients: a one-year, prospective consecutive study. Critical Care Medicine. 1991; 19: 463-473.

Havill J H; Moore J E; Armistead S; Ullal R. Open heart surgery: intensive care component, clinical profile and costs over one year. New Zealand Medical Journal. 1992; 105: 3-5.

Heyland D K; Cook D J; Jaeschke R; Griffith L. Selective decontamination of the digestive tract. An overview. Chest. 1994; 105: 1221-29.

Hodgeson T A. Costs of illness in cost effectiveness analysis: a review of the methodology. Pharmacoeconomics. 1994; 6: 536-552.

Holt A W; Bersten A D; Fuller S; Pipers R K *et al*. Intensive care costing methodology: cost benefit analysis of mask continuous positive airway pressure for severe cardiogenic pulmonary oedema. Anaesthetics and Intensive Care. 1994; 22: 170- 174.

Hosmer D W; Lemeshow S. Applied Logistic Regression. New York: Wiley; 1989.

Hulstaert P F; Kox W. Introduction. The ICU: A cost benefit analysis. Miranda D R; Langrehr D ed. Holland: Elsevier Science Publishers (B.V.); 1986: 1-10.

Jacobs J; Wyatt S. Economic evaluation of cefoperazone therapy. Drug Intelligence and Clinical Pharmacy. 1987; 21: 373-379.

Jacobs S; Foweraker J E; Roberts S E. Effectiveness of selective decontamination of the digestive tract in an ICU with a policy encouraging a low gastric pH. Clinical Intensive Care. 1992; 3: 52-58.

Jennett B. High Technology Medicine. Benefits and burdens. Oxford: Oxford University Publishers; 1986.

Joshi N; Localio A R; Hamory B H. A predictive risk index for nosocomial pneumonia in the intensive care unit, The American Journal of Medicine. 1992: 93; 135-142.

Kappstein I; Schulgen G; Beyer U *et al.* Prolongation of hospital stay and extra costs due to ventilator-associated pneumonia in an intensive care unit, European Journal of Clinical Microbiology and Infectious Diseases. 1992: 11; 504-508.

Kennedy P. A Guide to Econometrics, 3rd Edition. Oxford: Blackwell; 1993.

Kerridge R K; Glasziou P P; Hillman K M. The use of 'Quality- adjusted life years' (QALYs) in intensive care. Journal of the Australian Society of Anaesthetists. 1995; [in print].

Kerver A J H; Rommes J H; Mevissen-Verhage E A E *et al.* Colonisation and infection in surgical intensive care patients- a prospective study, Intensive Care Medicine. 1987: 13; 347-351.

Kind P; Rosser R; Williams A. Valuation of quality of life: some psychometric evidence. In: Jones Lee M W (Ed). The value of life and safety. Amsterdam: North Holland Publishing Company; 1982.

King's fund panel. Intensive care in the United Kingdom. Anaesthesia. 1989; 44: 428-431.

Knaus W A; Draper E A; Wagner D P; Zimmerman J E. APACHE II-A severity of disease classification system. Critical Care Medicine. 1985; 13(10): 818-829.

Kollef M H. The role of selective digestive tract decontamination on mortality and respiratory tract infections. A meta-analysis. Chest. 1994; 105: 1101-08.

Koopmanschap M A; Rutten F F H. The impact of indirect costs on outcomes of health care programs. Health Economics. 1994; 3: 385-393.

Kreis D J; Augenstein D; Civetta J M; Gomez G A *et al.* Diagnosis related groups and the critically injured. Surgery, Gynaecology and Obstetrics. 1987; 4: 317-322.

Ledingham I; Alcock S R; Eastaway A T; McDonald J C *et al.* Triple regimen of selective decontamination of the digestive tract, systemic cefotaxime,and microbiological surveillance for prevention of acquired infection in intensive care. The Lancet. 1988; i: 785-790.

Leu H S; Kaiser D L; Mori M *et al.* Hospital-acquired pneumonia: attributable mortality and morbidity, American Journal of Epidemiology. 1989: 129(6); 1258-1267.

Light R J; Pillemer D B. Summing Up: The science of reviewing research. London: Harvard University Press; 1984.

Loes O; Smith-Erichsen N; Lind B. Intensive Care-Cost and Benefit. Acta Anaesthesiol. Scand. 1987; 31(Supplement 84): 3- 19.

Loirat Ph; Johanson W G; Van Saene H K F *et al.* Selective digestive decontamination in intensive care unit patients. Intensive Care Medicine. 1992; 18: 182-188.

Malek M; Lynch W; Wells N; Elliott T. A comparison of the costs of ceftazidime therapy and gentamicin combinations in three UK hospitals. Journal of Antimicrobial Chemotherapy. 1992; 29: 207-217.

Malstam J; Lind L. Therapeutic intervention scoring system (TISS) - a method for measuring workload and calculating costs in the ICU. Acta Anaesthesiol Scand. 1992; 36: 758-63.

Markowsky S J; Christie J. Pharmacoeconomics of selective decontamination of the digestive tract in intensive care patients. Pharmacoeconomics. 1994; 5: 361-366.

Martinez-Pelluz A E; Merino P; Bru M; Conejero R. Can selective digestive decontamination avoid the endotoxaemia and cytokine activation promoted by cardiopulmonary bypass? Critical Care Medicine. 1993; 21: 1684-91.

McClelland P; Murray A E; Williams P S; Van Saene H K F *et al.* Reducing sepsis in severe combined acute renal and respiratory failure by selective decontamination of the digestive tract. Critical Care Medicine. 1990; 18: 935-939.

McGuire A; Henderson J; Mooney G. The economics of health care. London: Routledge and Kegan Paul; 1988.

Meers P D; Ayliffe G A J; Emmerson A M, *et al.* Report on the national survey of infection in hospitals, Journal of Hospital Infection. 1981: 2(Supp).

Metcalfe A; McPherson K (Department of Public Health and Policy, London School of Hygiene and Tropical Medicine). Study of Provision of Health Care in England, 1993. London: Department of Health; 1995.

Miranda D R; Van Saene H K F; Stoutenbeek C P; Zandstra D F. Environment and costs in surgical intensive care units. Acta Anaesthesiologica Belgica. 1983; 3: 223-232.

Miranda D R; Langrehr D ed. Management of Intensive Care. Guidelines for Better Use of Resources. Holland: Elsevier Science Publishers (B.V.); 1990.

Molina CD; Martin MG; Cavanillas AB *et al.* Estimacion del coste de la infeccion nosocomial en una unidad de medicina intensiva, Medicina Clinica Barcelona. 1993: 100(9); 329-332.

Moore R D; Smith C R; Holloway J J; Lietman P S. Cefotaxime vs nafcillin and tobramycin for the treatment of serious infection. Archives of Internal Medicine. 1986; 146: 1153-1157.

Mulrow C D. Rationale for systematic reviews. British Medical Journal. 1994; 309: 597-599.

Mundt D J; Gage R W; Lemeshow S; Pastides H. Intensive care unit patient follow up. Archives of Internal Medicine. 1989; 149: 68-72.

Nardi G; Valentinis U; Proietti A; De Monte A. Epidemiological impact of prolonged systematic use of topical SDD on bacterial colonization of the tracheobronchial tree and antibiotic resistance. Intensive Care Medicine. 1993; 19: 273- 278.

Nicholas F; Le Gall J R; Alperovitch A; Loirat P *et al.* Influence of patients' age on survival, level of therapy and length of stay in intensive care units. Intensive Care Medicine. 1987; 13: 9-13.

Niebuhr H; Nahrstedt U; Ruckert K; Kaiser W; Mosebach B; Hoffmann P. Empirische Therapie der nosokomialen oder ambulant erworbenen bakteriellen Pneumonie. Ceftriaxon versus Cefotaxim. Chemotherapie Journal. 1993; 2: 28-35.

North Thames East Anglia Division. NHS Supplies Catalogue. London; 1994 Nov.

O'Brien B J; Drummond M F; Labelle R J; Willan A. In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. Medical Care. 1994; 32: 150-163.

Osborne M; Evans T W. Allocation of resources in intensive care: a transatlantic perspective. Lancet. 1994; 343: 778-780.

PAEEC (Spanish Group for the Epidemiological Analysis of Critical Patients). Quality of life: a tool for decision making in the ICU. Intensive Care Medicine. 1994; 20: 251-252.

Paladino J A; Fell R E. Pharmacoeconomic analysis of cefmenoxime dual individualisation in the treatment of nosocomial pneumonia. The Annals of Pharmacotherapy. 1994; 28: 384-389.

Palomar M; Barcenilla F; Alvarez F; Nava J. Prevencion de la neumonia nosocomial: descontaminacion digestiva selectiva y sulcralfato. Medicina Intensiva. 1992; 16: 81-85.

Parno J R; Teres D; Lemeshow S; Brown R B. Hospital charges and long term survival of ICU versus non-ICU patients. Critical Care Medicine. 1982; 10: 569-574.

Patel M S. An introduction to meta-analysis. Health Policy. 1989; 11: 79-85.

Patrick D L; Danis M; Southerland L I; Hong G. Quality of life following intensive care. Journal of General Internal Medicine. 1988; 3: 218-223.

Pesau B; Falger S; Berger E; Weimann J. Influence of age on outcome of mechanically ventilated patients in an intensive care unit. Critical Care Medicine. 1992; 20(4): 489-492.

Petros A J; Marshall J C; Van Saene H K F. Should morbidity replace mortality as an endpoint for clinical trials in intensive care? The Lancet. 1995; 345: 369-371.

Pugin J; Auckenthaler R; Lew D P; Suter P M. Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia. Journal of the American Medical Association. 1991; 265: 2704-2710.

Rapaport J; Teres D; Lemeshow S; Avrunin J S *et al.* Explaining variability of cost using a severity of illness measure for ICU patients. Medical Care. 1990; 28: 338-348.

Reeves C L (National Health Service Management Executive). [Letter to Regional general managers]. Department of Health, Leeds; 1993 Jul 21. Costing for Contracting.

Reidy J J; Ramsay G. Clinical trials of selective decontamination of the digestive tract: review. Critical Care Medicine. 1990; 18: 1449-1456.

Reisman D. The political economy of health care. Ipswich: St Martin's Press; 1993.

Rello J; Ausina V; Ricart M *et al.* Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia, Chest. 1993: 104; 1230-1235.

Ridley S; Biggam M; Stone P. Cost of Intensive Care. Anaesthesia. 1991; 46: 523-530.

Ridley S; Biggam M; Stone P. A cost-benefit analysis of intensive therapy. Anaesthesia. 1993; 48: 14-19.

Ridley S; Plenderleith L. Survival after intensive care. Anaesthesia. 1994; 49: 933-935.

Rocha L A; Martin M J; Pita S; Paz J *et al.* Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract. Intensive Care Medicine. 1992; 18: 398-404.

Rodriguez-Roldan J M; Altuna-Cuesta A; Lopez A; Carrillo A. Prevention of nosocomial lung infection in ventilated patients: use of an antimicrobial pharyngeal nonabsorbable paste. Critical Care Medicine. 1990; 18: 1239-1242.

Rolando N; Gimson A; Wade J; Philpott-Howard J. Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. Hepatology. 1993; 17: 196-201.

Rowan K M; Kerr J H; Major E; McPherson K. Intensive Care Society's APACHE II study in Britain and Ireland-I: Variations in case mix of adult admissions to general intensive care units and impact on outcome. British Medical Journal. 1993; 307: 972-7.

SA Health Commission. SA Intensive care costing and casemix classification study. Adelaide: KPMG Peat Marwick; 1994; Draft report volume 1.

Sage W M; Rosenthal M H; Silverman J F. Is intensive care worth it? An assessment of input and outcome for the critically ill. Critical Care Medicine. 1986; 14: 777-782.

Sandy R. Statistics for business and economics. New York: McGraw Hill; 1990.

Schapira D V; Studnicki J; Bradhem D D; Wolff P *et al.* Intensive care, survival and expense of treating critically ill cancer patients. Journal of the American Medical Association. 1993; 269: 783-786.

Schulman K A; Glick H A; Rubin H; Eisenberg J M. Cost- effectiveness of HA-1A monoclonal antibody for gram-negative sepsis. Journal of American Medical Association. 1991; 266: 3466- 3471.

Selective Decontamination of the Digestive Tract Trialists' Collaborative Group. Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract. British Medical Journal. 1993; 307: 525-32.

Sheldon T A; Long A F; Freemantle N; Song F. The ideal: enemy of the useful? Quality in Health Care. 1995; 4: 52-54.

Shiell A. A Pilot appraisal of the costs and outcomes of adult intensive care. (Health Economics Study Group, Birmingham University). 1989.

Singer M; Myers S; Hall G; Cohen S L; Armstrong R F. The cost of intensive care: a comparison on one unit between 1988 and 1991. Intensive Care Medicine. 1994; 20: 542-549.

Slatyer M A; James O F; Moore P G; Leeder S R. Costs, severity of illness and outcome in intensive care. Anaesthesia and intensive care. 1986; 14: 381-389.

Spencer R C. Epidemiology of infection in ICU's. Intensive Care Medicine. 1994; 20: S2-S6.

Spiby J. Health care technology in the United Kingdom. Health Policy. 1994; 30: 295-334.

Standing Group on Health Technology (Department of Health). 1994 Report. London: DOH; 1994 Jun.

Stevens R M; Teres D. Pneumonia in an intensive care unit: a 30 month experience. Archives of Internal Medicine. 1974; 134: 106-111.

Stoddart J C. National ITU Audit 1992/93. London: Royal College of Anaesthetists; 1993.

Stoutenbeek C P; van Saene H K F; Miranda D R; Zandstra D F. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Medicine. 1984; 10: 185-192.

Stoutenbeek C P; Van Saene H K F; Zandstra D F. The effect of oral non-absorbable antibiotics on the emergence of resistant bacteria in patients in an intensive care unit, Journal of Antimicrobial Chemotherapy. 1987: 19; 513-520.

Stoutenbeek C P; Van Saene H K F. Prevention of pneumonia by selective decontamination of the digestive tract. Intensive Care Medicine. 1992; 18: S18-S23.

Studenmund A H. Using econometrics: a practical guide. Washington: Harper Collins; 1992.

Suter P. Selective decontamination of the digestive tract. A randomised controlled trial (unpublished extract). Hopital Cantonal Universitaire de Geneve, Switzerland. 1993.

Suter P; Armaganidis A; Beaufils F; Bonfill X *et al.* Consensus Conference: Predicting outcome in ICU patients. Intensive Care Medicine. 1994; 20: 390-397.

Tetteroo G W M; Wagenvoort J H T; Castelein A; Tilanus H W. Selective decontamination to reduce gram-negative colonisation and infections after oesophageal resection. Lancet. 1990; 335: 704-707.

The Euroqol Group. Euroqol: a new facility for the measurement of health related quality of life. Health Policy. 1990; 16: 199-208.

Thibault G E; Mulley G A; Barnett G O; Goldstein R L. Medical Intensive care-indications, interventions, and outcomes. New England Journal of Medicine. 1980; 302: 938-42.

Thoner J. Outcome and costs of intensive care. A follow-up study on patients requiring prolonged mechanical ventilation. Acta Anaesthesiol Scand. 1987; 31: 693-698.

Trilla A. Epidemiology of nosocomial infections in adult intensive care units. Intensive Care Medicine. 1994; 20: s1-s4.

Tsevat J; Dawson N V; Matchar D B. Assessing quality of life and preferences in the seriously ill using utility theory. Journal of Clinical Epidemiology. 1990; 43(Suppl): 73s-77s.

Ulrich C; Harinck-de Weerd J E; Bakker N C; Jacz K *et al.* Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections: a prospective randomized study. Intensive Care Medicine. 1989; 15: 424-431.

Unertl K; Ruckdeschel G; Selbmann H K; Jensen U *et al.* Prevention of colonization and respiratory infections in long-term ventilated patients by local antimicrobial prophylaxis. Intensive Care Medicine. 1987; 13: 106-113.

Vandenbroucke-Grauls C M; Vandenbroucke J P. Effect of selective decontamination of the digestive tract on respiratory tract infections and mortality in the intensive care unit. The Lancet. 1991; 338: 859-62.

Verhaegen J. Randomised study of selective digestive decontamination on colonisation and prevention of infections in mechanically ventilated patients in the ICU. Leuven: Katholieke Universiteit Leuven; 1992.

Vincent J L; Bihari D J; Suter P M; Bruining H A. The prevalence of nosocomial infection in intensive care units in Europe. Journal of the American Medical Association. 1995; 274: 639-644.

Wagner D P; Wineland T D; Knaus W A. The hidden costs of treating severely ill patients: charges and resource consumption in an intensive care unit. Health Care Financing Review. 1983; 5: 81-86.

Weinstein R C; Feinberg H V. Clinical Decision Analysis. Philadelphia: W B Saunders; 1980.

Wenzel R P. Hospital-acquired pneumonia: overview of the current state of the art for prevention and control. European Journal for Clinical Microbiology and Infectious Diseases. 1989; 8: 56-60.

White M C. Mortality associated with nosocomial infections: analysis of multiple cause-of-death data. Journal of Clinical Epidemiology. 1993; 46: 95-100.

Williams A. The cost benefit approach to the evaluation of intensive care units. The ICU: A cost benefit analysis. Miranda D R; Langrehr D ed. Holland: Elsevier Science Publishers (B.V.); 1986: 131-143.

Winter R; Humphreys H; Pick A; MacGowan A P *et al.* A controlled trial of selective decontamination of the digestive tract in intensive care and its effect on nosocomial infection. Journal of Antimicrobial Chemotherapy. 1992; 30: 73-87.

Wu A W; Rubin H R; Rosen M J. Are Elderly People Less Responsive to Intensive Care? Journal of American Geriatric Society. 1990; 38: 621-627.

Zaren B; Bergstrom, R. Survival of intensive care patients I: prognostic factors from the patients medical history. Acta Anaesthesiol Scand. 1988; 32: 93-100.

Zobel G; Kuttnig M; Grubbauer H; Semmelrock H *et al.* Reduction of colonization and infection rate during pediatric intensive care by selective decontamination of the digestive tract. Critical Care Medicine. 1991; 19: 1242-1246.

Appendix 2.1 Classification of Intensive Care Patients [Cullen *et al*, 1974]

Prior to the introduction of severity of illness scoring systems such as APACHE II, the following system was devised by Cullen *et al* [1974] to classify intensive care patients.

Class I: Surgical patients admitted to the routine recovery room for wake-up from anaesthesia and do not require intensive care

Class II: Patients physiologically stable requiring prophylactic overnight observation

Class III: Patients physiologically stable requiring intensive monitoring and nursing (frequently of an invasive nature); their condition is expected to remain stable or improve with possible return to general ward care the following day

Class IV: Patients physiologically unstable requiring intensive nursing and physician care with frequent observations and change of orders by surgeons, anaesthetists and internists; these patients usually have one or more of their organ systems disordered by disease processes and their prognoses are unpredictable and unstable.

The TISS scores of the four groups increase with the severity of illness of the patient:

Class	TISS Score (SEM)
I	5 (0.2)
II	11 (0.7)
III	23 (1.0)
IV	43 (1.0)

Appendix 2.2 Intensive Care Society Nurse Dependency Scoring System [ICS Audit, 1992/93]

The following scores are attributed to each ICU patient at the end of each nursing shift:

Dependency score	*Patient Type*
C	Closed bed
0	Staffed but empty bed
0.5	Spontaneously breathing for simple monitoring, perhaps post operative with opiate epidural or similar.
1	Artificially ventilated patient.
1.5	Ventilated patient receiving multiple infusions or requiring complex monitoring or needing very frequent endotracheal suction
2	As above but with very unstable cardiovascular system requiring frequent intervention, or, as above but with the addition of dialysis, haemofiltration, plasma exchange or other extracorporeal circuitry.

Appendix 2.3 Summary of Published Quality of Life Studies of Intensive Care

First Author	Details of Quality of Life Measures	Results reported
Cullen [1976] US n=62	4 unvalidated functional states measured prospectively 1,3,6,12 months post admission by telephone interview.	At 12 months: **Patient condition:** 41% full recovery **Mental status:** 89% fully alert **Functional state:** 55% freely ambulatory **Degree of productivity:** 42% functioning as before illness
Bams [1985] Holland n=238	Unvalidated degree of capacity measured retrospectively 2 years post discharge. Information from GP.	**Functional status at 2 years:** 74% returned to work 10% handicapped, but self-reliant 1.3% dependent on others
Sage [1985] US n=337	SIP (validated objective measure) and Uniscale (validated subjective measure) measured prospectively 16 to 20 months post discharge by postal questionnaire.	**Post ICU quality of life** Mean SIP score: 6.8% (sd=0.7%) Physical subscore: 4.5% (sd=0.7%) Psychosocial subscore: 6.4% (sd=0.8%) Mean Uniscale score: 7.6 (sd=0.3)
Slatyer [1986], Australia n=100	Spitzer QL Index[1] (validated objective and subjective) measured retrospectively 1 month before admission and prospectively 1 month afterwards by interview. 4 unvalidated functional states [Cullen, 1976] measured by interview.	QL-Index: little or no decrease. Cullen [1976] outcome assessment: **Patient condition:** 31% full recovery **Mental status:** 55% fully alert **Functional state:** 52% freely ambulatory **Degree of productivity:** 28% functioning as before illness
Loes [1987], Norway n=419	Safar Overall Performance Indicators[2] (previously reported measure) Patient satisfaction (unvalidated) measured 20 months post discharge by telephone	OPC 1: 72.2% OPC 2: 24.7% 95.6% 'completely satisfied'. 66% regarded themselves as completely recovered.
Thoner [1987], Norway n=109	4 functional categories (not validated) measured 49 months post discharge by postal questionnaire[3]	Patients in each category: Group I and II: 58.7% Group III: 27.4% Group IV: 15.1%

Appendix 2.3 (cont.)

First Author	Details of Quality of Life Measures	Results reported
Zaren [1987] Sweden n=717	Disability ranking (unvalidated modification Glasgow Outcome Scale[4]), working status retrospectively 3 months before 12 months post discharge	Patients living at home before and after ICU (90% vs 86%), leading an independent life (94% vs 88%).
Jacobs [1988], Holland n=118	Housing, drug use, hospital admissions, physical condition, functional status (unvalidated) retrospectively before admission 2 years post discharge (postal)	Before ICU vs After ICU: Drug use: 37% vs 56% (p=0.02) Hosp admissions:22% vs 39% p<0.01 Physical complaints: 21% deteriorated, 77% unchanged, 2% improved.
Patrick [1988], US n=69	SIP (validated objective measure) PGWB schedule[5] (validated affective measure) PQOL[6] (subjective measure validated by this study) measured 19 months post discharge by interview	SIP mean score: 15 (sd=14), general population score: 3.5 PGWB mean score: 37.7 (sd=9), population score: 39.1 PGWB: 59% rated health 'fair to very poor' compared with 30% general population. PQOL: mean score: 75 (sd=18), population score: 79 (sd=14)
Mundt [1989], US n=887	Employment status and modified unvalidated SIP (physical, psychological, social measure) preadmission and 6 months post discharge by postal questionnaire	Changes pre and 6 months post discharge: Working: 50% vs 36% Decrease in ability to think clearly and concentrate, decrease in ability to do housework, deterioration in all social variables (p<0.05)
Shiell [1989], UK n=82	NHP Rosser and Kind QoL Index (validated) measured post discharge by postal questionnaire	Comparison with population: 31% problems with work vs 7% 45% social life problems vs 10% 22% disability, 18% distress

Appendix 2.3 (cont.)

First Author	Details of Quality of Life Measures	Results reported
Yinnon [1989], Israel n=126	Karnofsky Index[7] (physical performance measure); Linear analogue self assessment (LASA)[8]; Sleep index[9]; Employment; Sexual activity.	Pre admission vs 6 month post discharge mean scores (sd): Karnofsky: 8.2 (1.7) vs 7.9 (2.0) LASA: 68 (15) vs 71 (20) Sleep index: 2.4 (0.5) vs 2.5 (0.4)
Ridley [1990], UK n=129	Rosser's disability categories Patrick's perceived quality of life score Katz's activities of daily living measured by postal questionnaire pre admission and post discharge	Groups suffering decrease in QoL ($p<0.05$) : Disability categories I or II (good QoL) Employment status (fully employed) Patients < 30 years old Trauma victims No other groups showed changes.
Vasquez [1992], Spain n=444	Previously published quality of life tool[10] (functional measure) postal questionnaire pre admission and 12 months post discharge	Patients at each QoL level (%) Level — Pre admission — After 1 year I — 28.2 — 12.4 II — 37.6 — 42.6 III — 23.9 — 28.2 IV — 10.4 — 16.2 No significance tests reported
Bell [1994] UK n=60	NHP measured on admission (in elective patients) and postal questionnaire 3 months post discharge	No significant changes in functional ability. 32% patients rated health 'worsened' 77% patients employment status no change
Kerridge [1995] Australia n=136	Unstructured questionnaire Rosser questionnaire both by interview and by telephone/post 3 years post discharge.	Health problems: None: 25%; minor: 48%; major: 16%; severe: 13%. Psychological sequelae: some: 26%; lots of: 6%. Rosser QoL index: range 0.70 to 0.99

Footnotes to Appendix 2.3

[1]**Spitzer QL-Index:** contains five dimensions: activity (involvement in own occupation); activities of daily living; perception of one's own health; support of family and friends; outlook on life.

[2] Safar Overall Performance Categories

OPC 1: Good overall performance: healthy, alert, capable of normal life

OPC 2: Moderate overall disability: conscious, moderate cerebral disability or moderate disability from non-cerebral system dysfunction alone, or both. Performs independent activities of daily life, but is disabled for competitive work.

OPC 3: Severe overall disability: conscious, severe cerebral disability or severe disability from non-cerebral organ systems dysfunction alone, or both. Dependent on others for daily support.

OPC 4: Coma or vegetative state.

OPC 5: Brain death.

[3] Thoner functional categories:

Group I: In good health. No sequelae

Group II: Minor physical or mental disturbance without occupational limitation. Some temporary economical support.

Group III: Moderate physical and/or mental disturbance(s) with occupational limitation. Permanent economical support.

Group IV: Severe physical and/or mental disturbance(s). Institutionalised.

[4]**Modified Glasgow Outcome Scale**

Three stages of increasing disability:

1. Good health, no limitation in daily activities;
2. Some limitations in daily activities but able to live an independent life;
3. Severe limitations in daily activities, not able to live an independent life.

[5]**PGWB Schedule** [Dupuy, 1984]: Psychological general well-being schedule used to assess patient's affective status. The PGWB consists of ten questions about perceptions of well-being during the month prior to interview such as happiness, sadness and control of mood that are measured on a five-point scale. A single summated score ranging from 0 (highly negative affect) to 50 (highly positive affect) was calculated. General health perceptions are also measured using a five-point self-rating of health during the preceding month, ranging from excellent to very poor.

[6]**PQOL**: Perceived Quality of Life Scale developed by Patrick [1988]. This is a cognitive measure of life quality or need satisfaction. Respondents are asked to rate their satisfaction on a scale from 0 to 100, with 11 items describing fundamental needs of daily living. Higher scores indicate greater satisfaction. An average of these summated ratings, the PQOL score, is calculated for each respondent.

Example: 'How satisfied are you on a scale of 0-100 with.....'

1. The health of your body
2. Your ability to think and remember

[7]Karnofsky Scale

Measures physical activity with scores ranging from 10 for normally active patients to 0 for the patient completely dependent on outside help. Limited physical activity means that the patient is unable to engage in strenuous physical activity but can perform regular daily activities such as walking and is fully independent in activities involved in self care. Minimal physical activity means that the patient is unable to perform normal physical activity but is partially able to take care of themselves in activities such as feeding, washing or use of the toilet without help.

[8]Linear Analogue Self-Assessment (LASA) score

This is a subjective score first introduced for use in cancer patients receiving chemotherapy. A position is indicated by the patient using a scale ranging from 0 (very bad) to 100 (very good) in relation to the following variables: general feeling of wellbeing, mood, level of social activity, pain, nausea, appetite, perceived ability to perform housework, level of anxiety and the patient's own perception of response to treatment. The mathematical expression of the mean LASA score ranges from 0 to 100.

[9]Sleep Index

Evaluated by three variables: duration ranging from more than 6 hours (3 points), 4 to 6 hours (2 points) or less than 4 hours (1 point): and depth of sleep ranging from sound (3 points), intermediate (2 points) and light (1 point). The mathematical average of these three variables in a given patient was designated the sleep index. A sleep index below 2 was considered to indicate sleep of poor quality.

[10]**Quality of Life Questionnaire [Vasquez, 1992]**

Consists of seven items:

The ability to have oral communication (0 to 8 points)

Sphincter control (0 to 6 points)

Capacity for making precise movements (0 to 3 points)

Capacity for physical exercise (0 to 3 points)

Mobility and dependence on others (0 to 12 points)

The need for regular medication (0 to 2 points)

Capacity to work or to perform activities usual for the retired (0 to 3 points).

Level I (total score 0), quality of life is normal

Level II (total score 1 to 5), there is mild deterioration in the quality of life, with regular use of medication as the most characteristic feature.

Level III (total score 6 to 10), there is significant deterioration in quality of life, usually implying changes in employment or in the activities of the retired, along with deterioration in capacity for physical effort.

Level IV (total score >10), scores usually correspond to a major handicap.

Appendix 3.1 Year of Publication, Country of Origin, Design of Study and Type of SDD Used in Published SDD Trials (authors listed in chronological order)

Trial (1st Authors)	Year published	Country of origin	Study design	SDD Regimes Used	Parenteral prophylaxis
Stoutenbeek	1984	Holland	Historical control	PTA (Tobramycin, Colistin, Amphotericin) paste and liquid qds for entire ICU stay	Cefotaxime 50mg/kg/day until decontamination achieved
Unertl	1987	Germany	RCT	Polymixin B, Gentamicin, Amphotericin paste and liquid qds for entire ICU stay	None
Kerver	1988	Holland	RCT	PTA paste and liquid qds for entire ICU stay	Cefotaxime 50mg/kg/day for 5 to 7 days
Ledingham	1988	UK	Consecutive control	PTA paste and liquid qds for entire ICU stay	Cefotaxime 50mg/kg/day for 4 days
Aerdts	1989	Holland	RCT: APACHE stratification	Norfloxacin, Colistin, Amphotericin paste and liquid qds for entire ICU stay	Cefotaxime 500mg tds for 5 days
Brun-Buisson	1989	France	Consecutive control and RCT	Nalidixic acid, Colistin, Neomycin liquid qds (length of treatment not stated), also oral disinfection with povidone-iodine tds in all patients.	None
Ulrich	1989	Holland	RCT	Norfloxacin, Colistin, Amphotericin paste and liquid qds for entire ICU stay	Trimethoprim 500mg od until decontamination achieved

Appendix 3.1 (cont.)

Trial (1st Authors)	Year published	Country of origin	Study design	SDD Regimes Used	Parenteral prophylaxis
Flaherty	1990	USA	RCT of SDD vs Sucralfate	Colistin, Gentamicin, Nystatin paste and liquid qds for entire ICU stay	None
Godard	1990	France	RCT, crossover, placebo, blind	All patients had Amphotericin, all intubated patients' oronasopharynx rinsed 6x daily with sodium bicarbonate and povidone-iodine SDD: Tobramycin, Colistin liquid qds (length not stated)	None
MacClelland	1990	UK	Consecutive control	PTA paste and liquid qds until extubation	Cefotaxime 1g qds for 4 days
Rodriguez-Roldan	1990	Spain	RCT, placebo, blind	PTA paste qds (length of treatment not stated). Oral disinfection in all patients with chlorhexidine 0.1% qds	None
Tetteroo	1990	Holland	RCT	PTA paste and liquid qds for 10 days post surgery	Cefotaxime 1g qds for 3 days prior to surgery
Blair	1991	UK	RCT: APACHE stratification	PTA gel and liquid qds for entire ICU stay	Cefotaxime 50mg/kg/day for 4 days
Fox	1991	UK	Consecutive control	PTA liquid only qds for entire ICU stay	Cephradine 60mg/kg/day for 4 days

Appendix 3.1 (cont.)

Trial (1st Authors)	Year published	Country of origin	Study design	SDD Regimes Used	Parenteral prophylaxis
Gaussorgues	1991	France	RCT	Gentamicin, Colistin, Vancomycin, Amphotericin qds liquid until extubated. All patients had oral and nasal disinfection with Amphotericin/Chlorhexidine or povidone-iodine 2%.	None
Hartenauer	1991	Germany	Crossover[1] placebo, blind	PTA paste and liquid qds for entire ICU stay	Cefotaxime 6g/day for 4 days (all patients in study)
Palomar	1991	Spain	RCT with nothing and sucralfate	PTA paste and liquid qds until extubated	Cefotaxime 1g tds for 4 days (SDD and sucralfate groups)
Pugin	1991	Switzerland	RCT, placebo, blind	Polymixin B, Neomycin, Vancomycin liquid six times daily until extubated	None
Zobel (paediatric)	1991	Austria	RCT	Colistin, Gentamicin, Amphotericin paste/gel and liquid qds for entire ICU stay	Cefotaxime 100mg/kg/day (length of treatment not stated)
Cerra	1992	USA	RCT, placebo, blind	Norfloxacin, Nystatin liquid qds for 5 days or for entire ICU stay	None

Appendix 3.1 (cont.)

Trial (1st Authors)	Year published	Country of origin	Study design	SDD Regimes Used	Parenteral prophylaxis
Cockerill	1992	USA	RCT	Gentamicin, Colistin, Nystatin paste and liquid qds for entire ICU stay	Cefotaxime 1g tds for 3 days
Gastinne	1992	France	RCT, placebo, blind	PTA paste and liquid qds until extubated	Cefotaxime 1g tds for 3 days
Hammond	1992	South Africa	RCT, placebo, blind	PTA gel and liquid qds until 48 hours after extubation	None
Jacobs	1992	UK	RCT	PTA paste and liquid qds until extubation	Cefotaxime 50mg/kg/day for 4 days
Rocha	1992	Spain	RCT, placebo, blind	PTA paste and liquid qds for entire ICU stay	Cefotaxime 6g/day for 4 days
Verhaegen (thesis)	1992	Belgium	RCT (control & 2 treatment groups)	Group 1: Ofloxacin, Amphotericin paste and liquid qds for entire ICU stay Group 2: PTA paste and liquid qds for entire ICU stay	Ofloxacin 200mg od for 4 days Cefotaxime 1g qds for 4 days
Winter	1992	UK	Consecutive control & RCT	PTA gel and liquid qds for entire ICU stay	Ceftazidime 50mg/kg/day for 3 days

Appendix 3.1 (cont.)

Trial (1st Authors)	Year published	Country of origin	Study design	SDD Regimes Used	Parenteral prophylaxis
de Champs	1993	France	Consecutive & contemporane-ous control	Erythromycin 1g liquid tds for entire ICU stay	None
Ferrer	1993	Spain	RCT, placebo, blind	PTA paste and liquid qds until extubation	Cefotaxime 8g/day for 4 days
Garcia	1993	Spain	RCT, placebo, blind	Gentamicin, Colistin, Amphotericin paste and liquid qds until extubation	Ceftriaxone 2g/day for 3 days
Gow (abstract)	1993	UK	Consecutive control	PTA gel and liquid qds until extubation	Cefotaxime 6g/day for 4 days
Korinek	1993	France	RCT, placebo, blind	PTA and Vancomycin paste and PTA liquid qds for 15 days	None
Martinez-Pelluz	1993	Spain	RCT	PTA liquid qds prior to operation (24-96 hours)	None

Appendix 3.1 (cont.)

Trial (1st Authors)	Year published	Country of origin	Study design	SDD Regimes Used	Parenteral prophylaxis
Nardi	1993	Italy	consecutive control	PTA paste and liquid qds until extubation	None
Rolando	1993	UK	RCT with cefuroxime[2]	PTA paste and liquid qds, Mupirocin 2% ointment qds to anterior nares for entire ICU stay, Clotrimazole 5g vaginally on admission and weekly thereafter to female patients	Cefuroxime 4.5g/day for 4 days
Suter (abstract)	1993?	Switzerland	RCT, placebo, blind	Polymixin B, Neomycin, Vancomycin liquid qds until extubation	None

[1] Crossover study between two ICUs in one hospital. ICU I received SDD for six months then was control for six months. ICU II was control for six months, then received SDD for six months. ICU I: Neurosurgical and cardiothoracic patients; ICU II: General surgery and multiple trauma

[2] Group 1: Infected on admission, received cefuroxime;

Group 2: Infected on admission, received SDD;

Group 3: Not infected on admission, received SDD

Group 4: Not infected on admission, received no initial antibiotics

Appendix 3.2 Patient Inclusion Criteria and Group Size in Published SDD Trials

Trials (Authors)	Patient Inclusion Criteria	Control group size	Treatment group size
Stoutenbeek	> 5 days ICU stay, ventilated, multiple trauma excluded if infected on admission	59	63
Unertl	Ventilated > 6 days, excluded patients with infection on admission	20	19
Kerver	> 5 days ICU stay, ventilated	49	48
Ledingham	All admissions	161	163
Aerdts	Ventilated > 5 days	18, 21[1]	17
Brun-Buisson	> 2 days ICU stay	Grp 1: 124; Grp 2: 50[2]	36
Ulrich	> 5 days ICU stay	52	48
Flaherty	Ventilated > 1 day	56	51
Godard	All admissions	84	97
MacClelland	Ventilated requiring renal replacement > 5 days	12	15
Rodriguez-Roldan	Ventilated	15	13
Tetteroo	Post oesophageal resection for oesophageal cancer	56	56

Appendix 3.2 (cont.)

Trials (authors)	Patient inclusion criteria	Control group size	Trial Group Size
Blair	> 2 day ICU stay (93% ventilated)	130	126
Fox	Ventilated > 4 days	12	12
Gaussorgues	Ventilated & receiving beta agonists	59	59
Hartenauer	Ventilated > 3 days, ICU stay > 5 days	101	99
Palomar	Ventilated > 4 days	31	26
Pugin	Ventilated, head or multiple trauma, pulmonary or cardiac failure	27	25
Zobel	ICU stay > 4 days	25	25
Cerra	ICU stay > 5 days	21	25
Cockerill	ICU stay > 3 days (excluded if infected on admission)	75	75
Gastinne	Ventilated > 1 day	225	220
Hammond	Ventilated > 2 days and ICU stay > 5 days	125	114

Appendix 3.2 (cont.)

Trials (authors)	Patient inclusion criteria	Control group size	Trial Group Size
Jacobs	Ventilated, ICU stay > 3 days	43	36
Rocha	Ventilated > 3 days, ICU stay > 5 days. Excluded if infected on admission	54	47
Verhaegen	Ventilated > 2 days	185	Grp 1: 193; Grp 2: 200
Winter	ICU stay > 2 days	Grp 1: 84; Grp 2: 92[3]	91
de Champs	ICU stay > 2 days	Grp 1: 34; Grp 2: 46[4]	43
Ferrer	Ventilated > 3 days	41	39
Garcia	Ventilated > 2 days	131	140
Gow	Ventilated > 2 days	60	67
Korinek	Ventilated > 5 days and no infection for 1st 5 days	60	63
Martinez	Elective coronary artery or valvular surgery	40	40

Appendix 3.2 (cont.)

Trials (authors)	Patient inclusion criteria	Control group size	Trial Group Size
Nardi	Ventilated > 3 days	170	332
Rolando	Fulminant liver failure	52	49
Suter	'Prolonged ventilation' after severe trauma or emergency surgery	35	36

[1] Group 1 patients receive any therapeutic antibiotics

Group 2 patients (and SDD patients) receive only those therapeutic antibiotics that do not disrupt microbial colonisation resistance (ie not penicillins)

[2] Group 1: historical control

Group 2: contemporaneous control

[3] Group 1: historical control

Group 2: contemporaneous control

[4] Group 1: historical control (Bays 1 and 3)

Group 2: contemporaneous control (Bay 3)

Treatment group: Bay 1

Appendix 3.3 Age and severity of illness and length of stay in Published SDD Trials

Trials (Authors)	Age: Mean (sd)		APACHE II score Mean (SD)	
	Control	SDD	Control	SDD
Stoutenbeek	37 (21)	35 (19)	ISS[1] 33.7 (13.1)	34.4 (14.9)
Unertl	median: 48 (range 8-73)	median: 53 (range 18-77)	SAPS[2] median:12 (range 5-17)	13 (4-18)
Kerver	56.1 (range 21-81)	55.2 (range 11-90)	15.1 (6.47)	14.6 (5.57)
Ledingham	52 (19)	51 (18)	13 (7.4)	14 (7.2)
Aerdts	49 (22); 46 (21)	45 (24)	22.6 (8.6); 23.4 (7.7)	20.5 (5.9)
Brun-Buisson	57 (18)	Grp 1: 60 (20) Grp 2: 58 (15)	Grp 1: 10.6 (4.1) Grp 2: 12.4 (4.6)	11 (4.1)
Ulrich	60.0 (18.2)	64.3 (16.3)	SAPS: 12.4 (5.3) ISS: 38.6 (16.9)	11.5 (4.8) 39.0 (11.1)
Flaherty	61	60	not reported	
Godard	51 (20)	47 (20)	not reported	

Appendix 3.3 (cont.)

Trials (Authors)	Age: Mean (sd)		APACHE II score Mean (SD)	
	Control	SDD	Control	SDD
MacClelland	54 (13)	51 (17)	16 (5)	21 (6)
Rodriguez-Roldan	49	54	18	16
Tetteroo	60.6 (range 42-78)	60 (range 40-77)	not reported	
Blair	46.5 (19.2)	49.3 (18.9)	median: 14	median: 14
Fox	57.6 (7.6)	57.3 (4.6)	not reported	
Gaussorgues	59 (16)	55 (16)	IGS[3]: 17 (3)	18 (3)
Hartenauer	ICU I: 55 (18) ICU II: 54 (17)	ICU I: 53 (17) ICU II: 52 (17)	ICU I: 10.1 (3.3) ICU II: 16.5 (10)	ICU I: 9.6 (3) ICU II: 13.2 (9)
Palomar	Control: 44.6 (19.2)	46.6 (17.8)	Control: 17.4 (4.6)	15.6 (4.6)

Appendix 3.3 (cont.)

Trials (Authors)	Age: Mean(SD)		APACHE II score mean (SD)	
	Control	SDD	Control	SDD
Pugin	46 (20)	45 (20.2)	14.7 (5.9)	15.8 (5.8)
Zobel	1.9 (0.5)	1.5 (0.5)	APCS[4]: 9.3 (1.9)	12.3 (1.7)
Cerra	Not reported		Not reported	
Cockerill	Not reported		18.3 (6.8)	18.6 (7.2)
Gastinne	53.9 (18.4)	55.7 (18.6)	SAPS: 13 (4)	14 (4)
Hammond	43.5 (16.5)	43.5 (15.5)	14.0 (7.1)	13.9 (8.4)
Jacobs	54.5 (18.9)	48.0 (16.7)	17.7 (7.4)	17.4 (7.5)

Appendix 3.3 (cont.)

Trials (Authors)	Age: Mean(SD)		APACHE II score mean (SD)	
	Control	SDD	Control	SDD
Rocha	44.1 (21)	42.8 (19)	16 (5)	14.9 (5)
Verhaegen	56.1 (16.9)	Grp 1: 56.5 (16.9) Grp 2: 55.6 (17.1)	18.3 (6.6)	Grp 1: 17.6 (6.3) Grp 2: 18.3 (6.6)
Winter	Grp 1: 59.9 Grp 2: 58.4	57.3	Grp 1: median: 13 Grp 2: median: 15	12 'significant difference'
de Champs	Grp 1: 53.9 (19.3) Grp 2: 53.4 (18.2)	56.5 (18.1)	SAPS: Grp 1: 10.6 (3.4) Grp 2: 10.2 (4.6)	10.6 (5.0)
Ferrer	59 (20)	62(18)	SAPS: 11.8 (3.6)	12.5 (4)
Garcia	54.5		26.0	
Gow	Not reported		'Significant difference, higher in SDD group'	

Appendix 3.3 (cont.)

Trials (Authors)	Age: Mean(SD)		APACHE II score mean (SD)	
	Control	SDD	Control	SDD
Korinek	46.6 (14.6)	44.4 (16)	SAPS: 10.8 (3)	11.0 (3)
Martinez-Pellus	57 (10)	52 (15)	7 (3)	7 (2)
Nardi	Not reported		Not reported	
Rolando	Grp 1: 30 (14) Grp 4: 35 (13)	Grp 2: 29 (8.8) Grp 3: 33 (12)	Not reported	
Suter	Not reported		Not reported	

[1] ISS (Injury Severity Scores)

[2] SAPS (Simplified Acute Physiology Score)

[3] IGS (Indice de Gravite Simplifie)

[4] APCS (Acute Physiologic Score for Children)

[5] SEM (standard error of the mean)

Appendix 3.4 Overall Infection Rates and Pneumonia Rates in Published SDD Trials

Trials (Authors)	Overall infection rate[1,2]		Pneumonia rate	
	Control	SDD	Control	SDD
Stoutenbeek	(48, 81%)	(10, 16%)*	35, 59%	5, 8%*
Unertl	14, 70%	4, 21%‡	9, 45%	1, 5%‡
Kerver	107, 218%	42, 88% *	40, 82%	6, 13%*
Ledingham	37, 24%	16, 10% ‡	18, 11%	3, 2% NST
Aerdts	not reported	not reported	Grp 1: 30, 166% Grp 2: 26, 124%	1, 6% *
Brun-Buisson	Grp 1: (35, 28%) Grp 2: (17, 33%)	(10, 28%) ns	(6, 9%)	(3, 5%) ns
Ulrich	not reported	not reported	(26, 46%)	(7, 13%) ††
Flaherty	19, 34%	7, 14% †	5, 9%	1, 2% NST
Godard	50, 60%	31, 32% †	8, 10%	0, 0% ‡

†p<0.05; ‡p<0.01; *p<0.001; ††p<0.0001.

Appendix 3.4 (cont.)

Trials	Overall infection rate[1,2]		Pneumonia rate	
Authors	Control	SDD	Control	SDD
MacClelland	17, 142%	7, 47% †	5, 42%	1, 7% †
Rodriguez-Roldan	not reported	not reported	14, 93%	3, 23% *
Tetteroo	51, 91%	18, 32% NST	8, 14%	1, 2% †
Blair	55, 42%	25, 20% ‡	45, 35%	12, 10% ‡
Fox	(6, 50%)	(8, 66%) ns	not reported	not reported
Gaussorgues	(15, 25%)	(5, 8%) †	not reported	not reported
Hartenauer	not reported	not reported	ICU I: 44, 72% ICU II: 21, 53%	ICU I: 5, 10% ICU II: 5, 10%*
Palomar	Control: 30, 97%	12, 46% ‡	Control: 22, 71%	6, 23%‡
Pugin	(21, 78%)	(4, 16%) ††	(24, 59%)	(4, 11%) NST
Zobel	(9, 36%)	(2, 8%) †	6, 24%	1, 4% NST

†$p<0.05$; ‡$p<0.01$; *$p<0.001$; ††$p<0.0001$.

Appendix 3.4 (cont.)

Trials	Overall infection rate[1,2]		Pneumonia rate	
Authors	Control	SDD	Control	SDD
Cerra	42, 200%	22, 88%*	23, 100%	14, 56% †
Cockerill	36, 48%	12, 16% †	14, 19%	4, 5% †
Gastinne	Not reported	Not reported	33, 15%	26, 12% ns
Hammond	64, 51%	44, 39% ns	(30, 24%)	(25, 22%) ns
Jacobs	Not reported	not reported	4, 9%	0, 0% NST
Rocha	88, 163%	21, 45%*	51, 94%	8, 17%*
Verhaegen	131, 71%	Grp 1: 72, 37%†† Grp 2: 151, 76% ns	38, 21%	Grp 1: 17, 9%† Grp 2: 28, 14% ns
Winter	Grp 1: (27, 32%) Grp 2: (32, 35%)	(3, 3%) ‡	Grp 1: 11, 13% Grp 2: 17, 18%	3, 3% NST
de Champs	Grp 1: (24, 71%) Grp 2: (23, 50%)	(19, 44%)	Grp 1: (14, 41%) Grp 2: (14, 30%)	(8, 19%) NST

†p<0.05; ‡p<0.01; *p<0.001; ††p<0.0001.

Appendix 3.4 (cont.)

Trials	Overall infection rate[1,2]		Pneumonia rate	
Authors	Control	SDD	Control	SDD
Ferrer	Not reported		10, 24%	6, 15% NST
Garcia	(46, 35%)	(25, 18%)[†]	79, 60%	29, 21% [*]
Gow	Not reported	Not reported	(9, 15%)	(12, 18%) NST
Korinek	71, 118%	36, 60% [‡]	25, 42%	15, 24% [†]
Martinez	Not reported	Not reported	Not reported	Not reported
Nardi	Not reported	Not reported	Not reported	Not reported
Rolando	25, 48%	17, 35% [‡]	5, 10%	3, 6% NST
Suter	Not reported	Not reported	(23, 67%)	(7, 20%)[*]

[†]$p<0.05$; [‡]$p<0.01$; [*]$p<0.001$; [††]$p<0.0001$.

[1] Infection rate reported is number of infections. Number of infected patients is listed in parentheses

[2] Definitions of Infection (Verhaegen [1993])

1. Respiratory infection: Purulent pulmonary secretions, new infiltrates on the chest X-rays and one of the following: fever/hypothermia, leukocytosis/leukopenia, physical examination, drop in arterial partial oxygen pressure. Bacteriologic diagnosis (two positive samples).

2. Urinary Tract infection: Urine culture with > 100,000 cfu/ml and > 3 leukocytes/high power field.

3. Wound infection: Inflammation and purulent secretion from the wound with positive culture.

4. Bacteraemia-sepsis: Positive blood culture associated with fever, leukocytosis and/or hypotension.

5. Catheter-associated sepsis: Same agent in blood and intravascular segment (no other sources of infection).

Appendix 3.5 Sub Group Analysis of Infections and Other Morbidity Measures Reported by SDD Trials

Trials	Sub Group Analysis of Infections		Morbidity Measures (means quoted)	
(Authors)	Control	SDD	Control	SDD
Stoutenbeek	None reported		None reported	
Unertl	None reported		Days intubated: 11	16 NST
Kerver	None reported		None reported	
Ledinghan	None reported		None reported	
Aerdts	None reported		None reported	
Brun-Buisson	None reported		None reported	
Ulrich	None reported		Days intubated: 7.8 Dialysis: 6 patients	10.7 ns 3 ns

Appendix 3.5 (cont.)

Trials	Sub Group Analysis of Infections		Morbidity Measures (means quoted)	
(Authors)	Control	SDD	Control	SDD
Flaherty	None reported		**Days intubated** with pneumonia: 5.6 no pneumonia: 1.2 **Days bladder catheterisation:** 3.8	 3.0 1.7 4.1
Godard	**Days to infection: 9** **Trauma: No. infections: 27** **Medical:No. infections: 7** **Surgical: No. infections: 16**	13* 21 ns 5 ns 5 ns	**Days intubated** 9 (sd: 12)	8 (sd: 12)
MacClelland	None reported		None reported	
Rodriguez-Roldan	None reported		**Days intubated: 10** **Days enterally fed: 6** **Days parenterally fed: 9**	11.7 5 8
Tetteroo	None reported		None reported	

Appendix 3.5 (cont.)

Trials (Authors)	Sub Group Analysis of Infections		Morbidity Measures (means quoted)	
	Control	SDD	Control	SDD
Blair	% infected patients: APACHE 0-9: 21 10-19: 32 20-29: 37 >30: 25	 15 ns 17 † 15 ns 25 ns	None reported	
Fox	None reported		**Days intubated: 9.5**	**11.3 ns**
Gaussorgues	None reported		**Days intubated: 17** **Days of beta agonists: 14**	**16 ns** **13 ns**
Hartenauer	None reported		None reported	
Palomar	None reported		None reported	
Pugin	None reported		None reported	
Zobel	None reported		**Days intubated: 10.1**	**10.4 ns**

Appendix 3.5 (cont.)

Trials (Authors)	Sub Group Analysis of Infections		Morbidity Measures (means quoted)	
	Control	SDD	Control	SDD
Cerra	None reported		No. developing ARDS[1]: 8 No. developing MOF[2]: 5	7 ns 6 ns
Cockerill	None reported		Days intubated: 10 Days of lines: 23 (30.9)	7 ns 19 (21.4)
Gastinne	None reported		Days intubated: 'no difference'	
Hammond	Trauma patients: No. infections: 16 APACHE 17-23: No. infections: 28	 17 ns 8[3]	No. patients: Ventilated: 125 Haemodialysis: 11 Chest drain: 42 Arterial line: 76 Peripheral line: 125 Central line: 116 Pulmonary catheter: 80 Parenteral feeding: 44 Enteral feeding: 117	 114 ns 8 ns 37 ns 56 ns 114 ns 99 ns 75 ns 32 ns 96 ns
Jacobs	None reported		None reported	

Appendix 3.5 (cont.)

Trials (Authors)	Sub Group Analysis of Infections		Morbidity Measures	
	Control	SDD	Control	SDD
Rocha	None reported		Days intubated: 13.2	13.1 ns
Verhaegen	No. infected patients: Grp. 1 Grp. 2 Polytrauma: 26/43 15/41 30/49† Cardiac surgery: 22/76 9/86 18/73‡ Vascular surgery: 8/16 4/13 8/20 ns Abdominal surg: 11/21 13/24 18/24 ns Oesophageal surg: 7/9 4/5 5/10 ns APACHE II <10: 8/21 7/28 11/19 ns 11-20: 48/99 27/111 53/114 ns 21-30: 29/58 18/51 24/59 ns >30: 4/7 2/3 6/8 ns		None reported	
Winter	None reported		None reported	
de Champs	None reported		None reported	
Ferrer	None reported		None reported	

Appendix 3.5 (cont.)

Trials	Sub Group Analysis of Infections		Morbidity Measures	
Authors	Control	SDD	Control	SDD
Garcia	None reported		**Days intubated survivors: 20**	**11[3]**
Gow	None reported		None reported	
Korinek	None reported		**Days intubated: 14.1**	**14.4 ns**
Martinez	None reported		None reported	
Nardi	None reported		None reported	
Rolando	None reported		None reported	
Suter	None reported		**Days intubated: 13.0**	**9.3[1]**

[1] ARDS Adult respiratory distress syndrome

[2] MOF Multi organ failure

[1]$p<0.05$; [2]$p<0.01$; [3]$p<0.001$; [4]$p<0.0001$.

Appendix 3.6 Mortality and Sub Group Analysis of Mortality Reported in SDD Trials

Trials (Authors)	Unit Mortality		Sub Group Mortality Analysis	
	Control	SDD	Control	SDD
Stoutenbeek	8 (13%)	3 (5%) ns	Not reported	
Unertl	6 (30%)	5 (26%) ns	Not reported	
Kerver	15 (32%)	14 (28.5%) ns	Not reported	
Ledingham	39 (24%)	39 (24%)	Trauma: 6/23 LOS >7 days: 12/35 APACHE II 17-33: 18/33	0/18‡ 5/39 ns 12/40 ns
Aerdts	Grp 1: 4/22% Grp 2: 2/9.5%	2 (12%) NST	Not reported	
Brun-Buisson	Grp 1: 13/26% Grp 2: 5/41.5%	52 (42%) NST	Not reported	
Ulrich	54%	31%†	Not reported	
Flaherty	'No difference'		Not reported	

Appendix 3.6 (cont.)

Trials	Unit Mortality		Sub Group Mortality Analysis	
(Authors)	Control	SDD	Control	SDD
Godard	12 (14%)	15 (15%) ns	Number of deaths: LOS <7 days: 5 LOS >7 days: 10 SAPS 0-10: 1 SAPS 11-20: 11 SAPS >21: 3 Trauma: 3 Medical: 6 Surgical: 6	 9 ns 2† 1 ns 4† 7 ns 7 ns 4 ns 1 ns
MacClelland	7 (58%)	9 (60%) ns	Not reported	
Rodriguez-Roldan	33%	30% ns	Not reported	
Tetteroo	2 (4%)	3 (5%) NST	Not reported	
Blair	18.8%	14.9%	LOS >2 days: 16.9% APACHE 10-19: 21.4%	13.5% ns 10.5% ns
Fox	8 (66.6%)	2 (16.7%)†	Not reported	
Gaussorgues	49%	49% ns	Not reported	

Appendix 3.6 (cont.)

Trials (Authors)	Unit Mortality		Sub group mortality analysis	
	Control	SDD	Control	SDD
Hartenauer	ICU I: 29/47.5% ICU II: 17/43%	ICU I: 19/38% ICU II: 15/31%	Not reported	
Palomar	Control: 29%	SDD: 27% ns	Trauma: 38%	0%†
Pugin	28%	26% ns	Not reported	
Zobel	2 (8%)	3 (12%) ns	Not reported	
Cerra	10 (48%)	13 (52%) ns	Not reported	
Cockerill	14 (19%)	8 (11%) ns	Hospital: 14 (19%)	8 (11%) NST
Gastinne	67 (30%)	75 (34%) ns	Hospital: 82 (36%)	88 (40%) ns
Hammond	15 (12%)	14 (12%) ns	Hospital: 21 (17%)	21 (18%) ns
Jacobs	53%	39% NST	APACHE 21-30: 67% 9-20: 53%	63% ns 35% ns

Appendix 3.6 (cont.)

Trials Authors	Unit Mortality		Sub group mortality analysis	
	Control	SDD	Control	SDD
Rocha	44%	21%[1]	Not reported	
Verhaegen	'No difference'		Not reported	
Winter	Grp 1: 40% Grp 2: 43%	36% NST	**Trauma (no. deaths):** Group 1: 1/19 Group 2: 4/10 **Vascular surgery:** Group 1: 7/19 Group 2: 4/17	4/12 NST 1/22 NST
de Champs	Grp 1: 4 (12%) Grp 2: 8 (17%)	4 (9%) NST	Not reported	
Ferrer	11 (27%)	12 (31%) ns	Not reported	
Garcia	47%	38% ns	Not reported	
Gow	'No difference'		Not reported	

Appendix 3.6 (cont.)

Trials Authors	Unit Mortality		Sub group mortality analysis	
	Control	SDD	Control	SDD
Korinek	7 (12%)	3 (5%) ns	Hospital: 11 (18%)	
Martinez	3 (8%)	1 (3%) ns	Not reported	
Nardi	Not reported		Not reported	
Rolando	27 (52%)	18 (27%) NST	Not reported	
Suter	'No difference'		Not reported	

[1]p<0.05; [2]p<0.01; [3]p<0.001; [11]p<0.0001.

Appendix 3.7 Resource Use and Unit Cost Information Reported by SDD Trials

Trials (Authors)	Length of ICU stay (mean)		Other Resource Use	
	Control	SDD	Control	SDD
Stoutenbeek	14	8 NST	None reported	
Unertl	median: 23	median 18 NST	None reported	
Kerver	20.1	16.9 NST	None reported	
Ledingham	Not reported		Antibiotic days: (excluding trial cefotaxime) 945	213 NST
Aerdts[1]	30 25	23 NST	Group 1: Group 2: Antibiotic days (mean): 42 26 Total antibiotic costs/ patient (DFl): 4022 1840 (1 DFl = US$0.50, 1989) Mean cost cultures/ patient (DFl): 618 575 Total costs (DFl): 4641 2415 Hospital charges: 70625 58393	13 (excluding cefotaxime)* 901 Cost of SDD per day: DFl 25.64 Cost of cefotaxime per day: DFl 46.74 Cost of SDD: DFl 855 420 Surveillance cultures: DFl 857 3036 54662

Appendix 3.7 (cont.)

Trials (Authors)	Length of ICU stay (mean)		Other Resource Use Information	
	Control	SDD	Control	SDD
Brun-Buisson	15	15 NST	None reported	
Ulrich	13.4	16.9 NST	None reported	
Flaherty	Not reported		Antibiotic days (excluding SDD): 414	114 NST Cost SDD per patient: $54 (US, 1990)
Godard	13	11 NST	Systemic antibiotic days excluding SDD: mean: 13	Mean: 8 NST
MacClelland	20	19 ns	No patients treated with antibiotics: No antibiotic: 0 Antistaphylococcal therapy: 58 Erythromycin: 17 Piperacillin: 83 Ampicillin: 66 Aminoglycoside: 100 Cefotaxime: 66	0 ns 80[#] 33[†] 53[‡] 33[‡] 73 ns 100 ns
Rodriguez-Roldan	Not reported		None reported	

Appendix 3.7 (cont.)

Trials (Authors)	Length of ICU stay (mean)		Other Resource Use Information	
	Control	SDD	Control	SDD
Tetteroo	4.9	5.5 ns	None reported	
Blair	7.5	7.6 ns	None reported	
Fox	11.7	11.3 ns	None reported	
Gaussorgues	19	16 NST	None reported	
Hartenauer	ICU I: 13.1 ICU II: 16.5	11.9 ns 13.2 ns	None reported	
Palomar	Not reported		None reported	
Pugin	14.7	12.8 ns	Antibiotic days (excluding SDD) mean: 4.1	mean: 1.6[†]
Zobel	13.5	13.7 ns	None reported	
Cerra	26	18 NST	None reported	

Appendix 3.7 (cont.)

Trials	Length of ICU stay		Other Resource Use Information	
(Authors)	Control	SDD	Control	SDD
Cockerill	12	10 ns	SDD course per patient: $212 (US, 1992)	
Gastinne	19	18 ns	Information from Pharmacie Centrale des Hopitaux de Paris Charge for therapeutic antibiotics per patient: control: mean: $577 (sd: 1051) Charge for antibiotics used to treat pneumonia: control: $158 Mean charge for all antibiotics including SDD: control: $577	SDD per day: $66.50 (US, 1992: 1$ =5.5Fr) Mean SDD charge per patient: $694 +/-544 $593 (sd: 1015) $53[†] $1287[*]
Hammond	16.8	16.2 ns	Tests & antibiotics for secondary infections/patient: control: $250	Acquisition costs SDD per patient: $500 (US, 1992) $400
Jacobs	10	9 ns	Cost per ICU bed/day: £1181.04 (UK, 1992)	
Rocha	17.8	18.8	Cost per ICU bed/day: 129151 ps (costs for staff, drugs disposables; charges for diagnostic tests, administration) Antibiotic costs per patient day (excluding SDD): 2736ps Cost per survivor: 3477246 ps	SDD course per day: 2785 ps (1 US$ = 107.11ps, 1989) 1334ps[†] 2582980ps

Appendix 3.7 (cont.)

Trials	Mean length of ICU stay		Other Resource Use Information	
(Authors)	Control	SDD	Control	SDD
Verhaegen	18.9	Grp I: 17.3 Grp II: 22.4 ns	Mean cost per ICU bed/day: BEF32000 (1990) Cost per urine culture: 60BEF Cost per bronchial aspirate culture: 160 BEF	Cost per SDD per patient (mean): 33793 BEF (22.4 days treatment with SDD and 4 days cefotaxime) Labour costs SDD preparation: 112 BEF SDD surveillance: 425BEF per surveillance (oropharynx, faeces, gastric aspirate)
Winter	Grp I: 7.3 Grp II: 8.0	6.4 NST	-	SDD course per day: £25 (UK, 1991) Ceftazidime per day: £57
de Champs	Grp I: 22.4 Grp II: 16.5	21.7 NST	None reported	
Ferrer	14.3	15.3 NST	None reported	
Garcia	'No significant difference'		None reported	

Appendix 3.7 (cont.)

Trials	Mean length of ICU stay		Other Resource Use Information	
(Authors)	Control	SDD	Control	SDD
Gow	Not reported		None reported	
Korinek	26.6	25.4 ns	Therapeutic antibiotic cost per infected patient: $361 (450) Total antibiotic cost per infected patient: $361 (450) Cost of parenteral antibiotics to treat pneumonia: $556 (506) Total cost per patient: $27383 Total cost per survivor: $33531	SDD cost per day: $70 (US, 1989) $418 (464) $1008 (545) due to 8.8 (3.3) days SDD $469 (413) ($1004 (506) including SDD) $25571 $29291
Martinez	3	3 ns	None reported	
Nardi	7.0	6.4 ns	None reported	
Rolando	'No significant difference'		None reported	
Suter	18.5	12.7[1]	($=1993 US$)	Mean cost reduction for SDD patients calculated at US$8510 per patient (95% CI: 153-16868[1])

[1] From thesis: Prevention of pneumonia in mechanically ventilated patients, Chap 6: cost effectiveness analysis (p.65-74), Aerdts SJA [1989].

[1]$p<0.05$; [2]$p<0.01$; [3]$p<0.001$; [11]$p<0.0001$.

Appendix 4.1 Trials Excluded from Extraction of Clinical Data

First author of study	Reason(s) for Exclusion of Study
Stoutenbeek 1984, Holland	Not RCT (historical control)
Ledingham 1988, UK	Not RCT (consecutive control)
Flaherty 1990, US	Not RCT (cross over study)
McClelland 1990, UK	Not RCT (historical control)
Tetteroo 1990, Holland	Atypical patient group (oesophageal resection for oesophageal cancer)
Fox 1991, UK	Not RCT (historical and consecutive controls)
Hartenauer 1991, Germany	Not RCT (consecutive control cross over study)
Zobel 1991, Austria	Atypical patient group (paediatric)
de Champs 1993, France	Not RCT (consecutive control) Unusual component (erythromycin)
Gow 1993, UK	Not RCT (consecutive control)
Martinez-Pelluz 1993, Spain	No clinical outcome measures (endotoxaemia & cytokine activation study)
Nardi 1993, Italy	Not RCT (consecutive control) No clinical outcome measures (tracheal colonisation & bacterial resistance study)
Rolando 1993, UK	Atypical patient group (fulminant liver failure)

Appendix 4.2 Summary Table of SDD Trials Included in Systematic Review

Trial author, date of publication and country of origin	Inclusion in systematic review models
Unertl [1987], Germany[1]	All, Mixed, Trauma[2]
Kerver [1988], Holland	All, Mixed, Trauma
Aerdts [1989], Holland	All, Mixed
Brun-Buisson [1989], France	All
Ulrich [1989], Holland	All, Mixed
Godard [1990], France	All, Mixed
Rodriguez-Roldan [1990], Spain	All, Mixed
Blair [1991], UK	All, Mixed, Trauma
Gaussorgues [1991], France	All
Palomar [1991], Spain	All, Mixed
Pugin [1991], Switzerland	All, Mixed
Cerra [1992], USA	All, Mixed, Trauma
Cockerill [1992], USA	All, Mixed, Trauma
Gastinne [1992], France	All, Mixed, Trauma
Hammond [1992], South Africa	All
Jacobs [1992], UK	All, Mixed
Rocha [1992], Spain	All, Mixed, Trauma

cont...

Summary Table of SDD Trials Included in Systematic Review (cont.)

Trial author, date of publication and country of origin	Inclusion in systematic review models
Verhaegen I [1992], Belgium	All, Mixed, Trauma
Verhaegen II [1992], Belgium	All, Mixed, Trauma
Winter [1992], UK	All, Mixed
Ferrer [1993], Spain	All
Garcia [1993], Spain	All
Korinek [1993], France	All, Mixed, Trauma
Suter [1993], Switzerland	All

[1] For more detail on individual trial design, refer to Chapter Three, Appendix 3.1.

[2] 'All': trial included in 'All ICU' model

'Mixed': trial included in 'Mixed ICU' model

'Trauma': trial included in 'Surgery/trauma ICU' model

Appendix 4.3 Fixed Effects Statistical Methods for Pooling Clinical Data (Colton [1991])

1. Pooled means and 95% confidence intervals for continuous variables.

Using binomial approximation to the normal distribution:

Mean of all studies = $1/N \Sigma(n_k x_k)$

Confidence intervals = mean +/- $t_{s/2}$ standard error of mean (SEM)

$SEM = 1/N \sqrt{\Sigma n_k^2 s_k^2}$

Where N = total number of observations: $n_1 + n_2 + ...n_k$ (where n = sample size)

x = sample mean

s = sample standard deviation

The conditions for use of this expression are that n_k is more than or equal to 5 and that the sample means are independent of one another.

2. Pooled means and 95% confidence intervals for non continuous variables.

Using binomial approximation to the normal distribution, the same expressions as above are used and the same conditions apply. Non-continuous variables such as proportions do not have variance in the same way as continuous normally distributed variables. The sample variance (s^2) can be derived from the following expression:

$s^2 = \Pi (1 - \Pi)$

where Π is the observed sample proportion or rate.

Therefore, SEM $= 1/N \sqrt{\Sigma n_k^2 (\Pi(1-\Pi)_k)}$

3. Effect size and 95% confidence intervals for non continuous variables.

Mean effect size $= 1/N \Sigma(n_k (\Pi_t-\Pi_c))$

where Π_t = sample proportion of treated group

Π_c = sample proportion of control group

For each sample:

$$\text{Standard error of effect size} = \sqrt{\frac{\Pi_t(1-\Pi_t)}{n_t} + \frac{\Pi_c(1-\Pi_c)}{n_c}}$$

For pooled values,

95% Confidence intervals = mean effect size $+/- t_{a/2}$ standard error of effect size

where standard error of mean effect size =

$$1/N \sqrt{\Sigma n_k^2 \left(\frac{\Pi_t(1-\Pi_t)}{n_t} + \frac{\Pi_c(1-\Pi_c)}{n_c}\right)}$$

Appendix 4.4 Inclusion Criteria in Clinical Trials Groups

This table summarises inclusion criteria for patients in SDD trials.

Inclusion criteria for patients in SDD trials	All trials No. trials	Mixed ICU model No. trials	Surgery/trauma model No. trials
All admissions	1	1	0
Vent. admissions	2	1	0
LOS > = 1 day	1 (1)*	1 (1)	1 (1)
LOS > = 2 days	6 (3)	4 (2)	3 (2)
LOS > = 3 days	4 (3)	3 (2)	1 (0)
LOS > = 4 days	1 (1)	1 (1)	0 (0)
LOS > = 5 days	7 (5)	6 (4)	4 (3)
LOS > = 6 days	1 (1)	1 (1)	1 (1)

*Numbers in parentheses indicate number of trials where the patients had to be ventilated to be included in the trial.

Appendix 4.5 Synthesis of Mortality Probabilities

This appendix summarises the algebraic method used to synthesise mortality probabilities from published evidence.

Let x = probability of mortality if infected

Let y = probability of mortality if uninfected.

In the 'all ICU' model, the base pneumonia rate is 29.4% and the base mortality is 29.5%.

If 1000 patients are admitted to ICU,

294 contract ICU-acquired pneumonia and x% die.

706 do not contract ICU-acquired pneumonia and y% die.

This can be expressed as: $294x + 706y$ = overall mortality (29.5%)

In the 'all ICU' model, the SDD treated pneumonia rate is 13.8% and the mortality is 26.7%.

If 1000 patients are admitted to ICU,

Assuming that the mortality from infection once it is acquired does not change between SDD-treated and non-SDD treated groups:

138 contract ICU-acquired pneumonia and x% die.

862 do not contract ICU-acquired pneumonia and y% die.

This can be expressed as: $138x + 862y =$ overall mortality (26.7%)

Solving these two equations for x and y produces an infected mortality of 42.3% and an uninfected mortality of 24.2%.

Appendix 4.6 Details of General Study Design in Clinical Trials Groups

Parameter	All trials n = 24	Mixed ICU model n = 18	Surgery/ trauma model n = 10
No. trials using parenteral therapy	14	11	6
No. trials using therapy for LOS	13	11	7
Trials using SDD whilst ventilated	8	4	1
No. trials using PSB	9	6	3
No. blinded trials	11	6	4

Appendix 4.7 Details of SDD Pharmaceutical Regimens in Clinical Trials Groups

Treatment details	All trials	Mixed ICU model	Surgery/ trauma model
No. trials using PTA paste & liquid	10	8	5
No. trials using PTA gel & liquid	4	3	1
Gentamicin substitution	4	1	1
Polymixin B substitution	3	2	0
Nalidixic acid substitution	1	1	0
Ofloxacin substitution	1	1	0

4 trials added in vancomycin to cover for MRSA.

Appendix 4.8 Details of Cefotaxime Protocols in Clinical Trials Groups

Cefotaxime dose details	All trials	Mixed ICU model	Surgery/ trauma model
1g tds 3 days	2	1	1
1g qds 4 days	3	3	2
1g qds 5-7 days	1	1	1
1g tds 4 days	1	1	0
2g tds 4 days	1	1	1
2g qds 4 days	1	0	0

Appendix 4.9 Costs of SDD Regimes Reported by SDD Trials

Aerdts (Holland, 1989): SDD (paste and liquid) and systemic cefotaxime per patient DFl 857 (439-1772) (one DFl = $0.50)

Flaherty (US, 1990): $54 per patient (Colistin, gentamicin, nystatin paste and liquid qds for entire ICU stay, no IV therapy, LOS not reported)

Gastinne (France, 1992): US$66.50 per day, mean charge per patient $694 +/-544 (information supplied by Pharmacie Centrale des Hopitaux de Paris) PTA paste and liquid until extubated, no IV therapy.

Hammond (South Africa, 1992): US$500 per patient (PTA gel and liquid qds until 48 hours after extubation, cefotaxime 1g tds for 3 days).

Rocha (Spain, 1992): US$26 per day (1989 $), (PTA paste and liquid qds for entire ICU stay, cefotaxime 6g/day for 4 days)

Verhaegen (Belgium, 1992): 33793 BEF per patient (=22.4 days SDD PTA paste and liquid qds for entire ICU stay and cefotaxime 1g qds for 4 days).
Labour costs in SDD production per patient: 112 BEF

Winter (UK, 1992): £25 per day (1991 prices) PTA gel and liquid qds for entire ICU stay

Korinek (France, 1993): US$70 per day (US, 1989); PTA and vancomycin paste and liquid qds for 15 days.

Appendix 4.10 Microbiological Surveillance Reported in the 24 Included SDD RCTs

Culture site	On admission	2x week	3x week
Oropharyngeal	16	9	5
Rectal	15	10	5
Urine	14	5	3
Tracheal aspirate	14	8	5
Gastric aspirate	10	9	3
Blood	4	1	0

Appendix 4.11 British Costs for Microbiological Surveillance (financial year 1994/5):

Swab site	Costs (1994/95)£
Oropharyngeal swab	4.96
Faecal/stool	12.13
Nose	3.58
Tracheal aspirate	8.82
Wound	7.72
Urine	4.41
Blood	11.03
Tobramycin level	12.68

NB: These are costs to the microbiology department only and include culturing for antibiotic sensitivity. Therefore, the decrease in positive cultures and subsequent decrease in need for susceptibility testing from SDD is not going to be reflected if these costs are used. The figures quoted are the prices charged by the microbiology department to external users of their services.

Appendix 4.12 Synthesis of Pneumonia-Attributable Length of Stay

This appendix summarises the algebraic method used to synthesise length of ICU stay attributable to pneumonia from published evidence. 14 trials report lengths of ICU stay for SDD-treated and non-SDD-treated patients. The weighted means are 18.03 days (sd = 9.85) for non-SDD treated and 17.51 days (sd = 10.62), calculated from 1309 patients.

Let x = length of ICU stay if infected
Let y = length of ICU stay if uninfected

The base pneumonia rate is 29.4% and the base length of stay is 18.0 days.

If 1000 patients are admitted to ICU,
294 contract pneumonia, 706 do not contract pneumonia and the mean length of stay is 18.0 days.
This can be expressed as: 294x + 706y = 18.0 days x 1000 patients

The SDD treated pneumonia rate is 13.8% and the length of stay is 17.5 days.

If 1000 patients are admitted to ICU,
138 contract pneumonia, 862 do not contract pneumonia and the mean length of stay is 17.5 days.
This can be expressed as: 138x + 862y = 17.5 days x 1000 patients

Solving these two equations for x and y produces an infected length of stay of 20.2 days and an uninfected length of stay of 17.1 days. The derived infection-attributable length of stay is 3.1 days.

Appendix 5.1 Clinician Questionnaire

Selective Decontamination of the Digestive Tract

1. How many admissions do you have in one year?

.....

2. How many of your patients stay longer than 3 days?

.....

3. Please indicate the percentage of your patients that are surgical:

.....

4. Do you use 'protected specimen brush technique' for obtaining sputum samples as a diagnostic technique? **Yes / No**

SDD is a form of infection control that is used to eliminate endogenous gut bacteria. It can consist of antimicrobial oropharyngeal pastes or gels, oral liquids or intravenous antibiotics, or a combination of two or all of these. It is also called SPEAR (Selective Parenteral and Enteral Antisepsis Regime).

5. Does your unit currently use SDD at all? **Yes / No**

If you have answered 'yes' to this question, please carry on to question 6. Otherwise go to question 8 on the other side of this sheet.

6. Do you give SDD to a) All patients **Yes / No**

If 'no', please outline inclusion or exclusion criteria:

(eg do you only use in mechanically ventilated, trauma, adult or other subsets of patients?)

.....

.....

7. How long has the unit been using SDD?

..... Don't Know_____

Go on to question 9 on the other side of this sheet.

Appendix 5.1 cont.

8. a) Has your unit, to your knowledge, ever used SDD? **Yes / No / Don't know**

b) If you have ever used SDD, when did you stop?

..... Don't know____

c) Tick the three main reasons why you do not use SDD:

No clearly proven benefit at the moment ☐

Financial constraints ☐

It is impractical and time consuming ☐

Microbiologist resistance ☐

Nursing resistance ☐

Did not know about it ☐

Other .....

9. Do you think that SDD:

	Agree	**Don't Know**	**Disagree**
a) Decreases respiratory infection incidence?	☐	☐	☐
b) Decreases length of stay?	☐	☐	☐
c) Decreases mortality?	☐	☐	☐
d) Increases outbreaks of multiresistant bacteria?	☐	☐	☐
e) Makes people more likely to follow other infection control policies?	☐	☐	☐

10. Does your unit carry out any of the following? (tick all boxes that apply)

a) Monitoring infection rates ☐

b) Severity of illness scoring and outcome audit ☐

c) Audit of SDD costs and/or outcomes. ☐

11. Have you seen the recent meta-analysis on selective digestive decontamination in the British Medical Journal (28th August 1993) **Yes / No**

Thank you very much for completing this questionnaire.

Appendix 5.2 Pharmacist Questionnaire

Selective Decontamination of the Digestive Tract (SDD)

1. Does your unit routinely use any of the following ulcer prophylaxis?
   Please tick which you use and indicate frequency:

	Usually	Sometimes	Never
Ranitidine	☐	☐	☐
Cimetidine	☐	☐	☐
Sucralfate	☐	☐	☐
Omeprazole	☐	☐	☐
Antacids	☐	☐	☐
No prophylaxis	☐	☐	☐

Other
(please give details)

.....

2. Which three antibiotic regimes would you most commonly use for a suspected gram negative infection?

1 ..... 2 ..... 3 .....

SDD is a form of infection control that is used to eliminate endogenous gut bacteria. It can consist of antimicrobial oropharyngeal pastes or gels, oral liquids or intravenous antibiotics, or a combination of two or all of these. It is also called SPEAR (Selective Parenteral and Enteral Antisepsis Regime).

3. Does your intensive care unit currently use SDD at all? **Yes / No**

If you have answered 'no' to this question, you do not need to continue with the questionnaire beyond question 3.
Otherwise go to question 4.

4. This question requires information about which SDD formulations you use.

Indicate whether you use an oral paste/gel and/or an oral liquid.

Our SDD regime contains: (tick appropriate boxes)

- an oral paste ☐
- an oral gel ☐
- an oral liquid ☐

Appendix 5.2 cont.

5. Tick the constituents in your oral paste/gel and oral liquid, giving details of doses if you know them. If the system you use is not on the list, please give details at the bottom.

Antibiotic	Paste/Gel	Dose	Oral Liquid	Dose
Tobramycin	☐	.....	☐	.....
Gentamicin	☐	.....	☐	.....
Amphotericin	☐	.....	☐	.....
Nystatin	☐	.....	☐	.....
Polymixin E (Colistin)	☐	.....	☐	.....
Neomycin	☐	.....	☐	.....
Others	☐	.....	☐	.....

6. How many times a day does the patient receive this treatment? .....

7. How long does the patient have this topical treatment?
(tick appropriate box and give extra details if necessary)

All the time they are on the intensive care unit ☐

A specified length of time from ICU admission ☐
(give details)

.....

8. How do you obtain these preparations? (Tick appropriate boxes)
* If you supply individual ingredients for the suspension please indicate which ones they are and how they are supplied.

	Bought ready made	**Manufactured by pharmacy**
Paste/gel	☐	☐
Suspension: Complete formulation	☐	☐
*Constituent 1.....	☐	☐
*Constituent 2.....	☐	☐
*Constituent 3.....	☐	☐

9. a) Do you use intravenous antibiotics in your SDD regime? **Yes / No**

b) If 'yes', please outline which antibiotic(s), usual dose and length of course

.....

Thank you very much for completing this questionnaire.

Appendix 5.3 Details of SDD Regimes Reported by Centres Using SDD

Hospital	*Patient group*[1]	*SDD Regime*	*Source*	*Duration of Treatment*	*Intravenous Antibiotics*	*Duration of Use*
1	Liver transplant (50)	Liquid: Amphotericin 500mg qds Colistin 100mg qds Neomycin 1g qds	Bought Bought Bought	Entire ICU stay	Piperacillin/ Tazobactam (6 doses)	10 months
2	Liver transplant (100)	Paste: Amphotericin 2% Colistin 2% Neomycin 2% qds Liquid: Amphotericin 500mg qds Colistin 100mg qds Neomycin 1g qds	Made Bought	Entire ICU stay	None	3 years
3	'High risk' (10)	Gel: PTA[2] qds Liquid: PTA[3] qds	Bought[4] Bought	Whilst ventilated	None	Not known

Appendix 5.3 (cont.)

Hospital	*Patient Group*[1]	*SDD Regime*	*Source*	*Duration of Treatment*	*Intravenous Antibiotics*	*Duration of Use*
4	Ventilated trauma & sepsis (8)	Paste: PTA qds Liquid: PTA qds	Made Made	Whilst ventilated	Cefotaxime	3 years
5	Ventilated trauma and burns (20)	Gel: PTA tds Liquid: PGA[5] tds	Bought[4] Bought	Whilst ventilated Until absorbing enteral feed	Cefotaxime 2g bd for 48 hours	3 years
6	'High risk' (4)	Paste: PGA qds Liquid: PGA qds	Made Bought	Entire ICU stay	None	18 months

Appendix 5.3 (cont.)

Hospital	*Patient Group*[1]	*SDD Regime*	*Source*	*Duration of Treatment*	*Intravenous Antibiotics*	*Duration of Use*
7	Ventilated >48 hours trauma (35)	Paste: PGA qds Liquid: PGA qds	Made Bought	Until extubation (or until absorbing enteral feed)	Cefotaxime 2g tds for 48 hours	5 years
8	Ventilated burns or trauma (10)	Gel: PTA qds Liquid: PTA qds	Made Bought	For entire ICU stay	Cefotaxime 2g tds for 72 hours	3-4 years
9	Ventilated trauma and burns (12)	Gel: PTA qds Liquid: PTA qds	Bought[4] Bought	Trauma: whilst ventilated Burns: for entire ICU stay	Cefotaxime 1g qds for 72 hours	3 years

Appendix 5.3 (cont.)

Hospital	*Patient Group*[1]	*SDD Regime*	*Source*	*Duration of Treatment*	*Intravenous Antibiotics*	*Duration of Use*
10	Ventilated (RCT)[4] (10/21)	Gel: PTA qds Liquid: PTA qds	Bought[4] Bought	Whilst ventilated	None	5 years
11	'High risk' (20)	Gel: PTA qds Liquid: PTA qds	Bought[4] Bought	Entire ICU stay	None	4 years
12	'High risk' (if microbiology advise) (3)	Paste: PTA qds Liquid: PTA qds	Made Bought	No standard length of time	Cefotaxime for 84 hours	5 years
13	Ventilated trauma patients (9)	Paste: PTA qds Liquid: PTA qds	Made Bought	Until absorbing enteral feed	Cefotaxime 50mg/kg per day	5 years

Appendix 5.3 (cont.)

Hospital	*Patient Group*[1]	*SDD Regime*	*Source*	*Duration of Treatment*	*Intravenous Antibiotics*	*Duration of Use*
14	Expected length of stay > 48 hours[6] (250)	Gel: PTA qds Liquid: PTA qds	Made Made	Entire ICU stay	Cefotaxime 1g qds for 96 hours	5 years
15	Ventilated 'high risk' (not known)	Paste: PTA qds Liquid: PTA qds	Made Bought	Whilst ventilated	None	< 1 year
16	Ventilated (not known)	Paste: PTA qds Liquid: PTA qds	Bought Bought	Whilst ventilated	Cefotaxime 50mg/kg per day for 4 to 7 days	2 years

[1] Number of patients treated with SDD per year in parentheses

[2] PTA paste/gel: Polymixin E 2%, Tobramycin 2%, Amphotericin 2%

[3] PTA liquid: Polymixin E 100mg, Tobramycin 80mg, Amphotericin 100mg

[4] Gel bought from Bristol Royal Infirmary Pharmacy Manufacturing Department

[5] Polymixin E, Gentamicin and Amphotericin (strengths and doses the same as PTA)

[6] Patients entered into a randomized controlled trial only

Appendix 6.1a Data Collected for Admissions Database

The data collected for each patient was:

Name
Hospital number
Sex
Origin
APACHE II score
Presence & source of infection
Elective admission?
Weight
Readmission to ICU (within last 6 months)
Date of hospital admission
Date and time of ICU admission
Admitting specialty
CPR?
Date and time of ICU discharge
Date of hospital discharge
Diagnosis

NHS number
Date of birth
Race
GP address and telephone no.
GCS score
Presence & source of cancer
Smoker (present, past, non)
Surgical admission
Chronic conditions
Admitting consultant
Iatrogenic events in surgery?
Destination on ICU discharge
Destination on hospital discharge
Reason for admission

Appendix 6.1b Data Collected for Daily Resource Use Database

Whilst the patient was on ICU, the following interventions and resource use associated with their stay was recorded daily:

1. Type of intubation and ventilation mode
2. Daily TISS score
3. Drugs, nutrition and blood products
4. Chemical pathology, haematology, microbiology[1] and radiology[2] tests
5. Physiotherapy and chest suction frequency
6. Intensity of monitoring (ie number of peripheral and central intravenous lines, arterial lines, pulmonary artery catheters, drains, nasogastric tube, urinary catheter, epidural catheter, ICP (intracranial pressure) bolt. Insertion and maintenance of these lines is recorded.
7. Events (surgery, haemodialysis, intubation, cardiac arrest, post mortem care, haemorrhage, ECG, EEG)
8. Daily APACHE II scores (LTH only)
9. Dependency scores for each shift (LTH only)
10. Infection status[3]

[1] Retrieved from the hospital computer system at LTH. At DGH, the results were notified by printed summaries in the notes.

[2] Retrieved retrospectively from radiology departments.

[3] Obtained from the medical notes, microbiological reports and discussion with medical staff.

Appendix 6.2 Summary of Admitting Diagnoses (Knaus *et al* [1985] APACHE II categories)

Diagnosis	DGH/%	LTH/%
Post peripheral vascular surgery	29 (21.0)	35 (16.5)
Post GI surgery for neoplasm	4 (2.9)	19 (9.0)
Post neurosurgery	0 (0.0)	26 (12.3)
Respiratory insufficiency post op	24 (17.4)	19 (9.0)
GI complications post op	8 (5.8)	14 (6.6)
Multiple/head trauma post op	5 (3.6)	12 (5.7)
Sepsis post op	5 (3.6)	7 (3.3)
Miscellaneous post op	6 (4.3)	9 (4.2)
Cardiac complications post op	6 (4.3)	8 (3.7)
Neurosurgery nonoperative	6 (4.3)	11 (5.2)
Resp insufficiency due to infection	11 (8.0)	11 (5.2)
Respiratory insufficiency (other)	9 (3.6)	11 (5.2)
Multiple/head trauma nonoperative	5 (3.6)	8 (3.7)
Sepsis nonoperative	0 (0.0)	4 (1.9)
Miscellaneous nonoperative	8 (5.8)	13 (6.1)
Cardiac complications nonoperative	12 (8.9)	5 (2.4)

Appendix 6.3 Cost per Nursing Shift at LTH and DGH

Nursing Grades	Cost (DGH)/£	Cost (LTH)/£	Nursing Grades	Cost (DGH)/£	Cost (LTH)/£
D	61.88	63.68	D long day	103.14	106.12
E	70.14	74.78	E long day	116.90	124.62
F	78.56	86.48	F long day	130.88	144.12
G	89.30	89.48	G long day	149.00	149.12
H	95.03	95.10	H long day	164.16	158.50
D night	86.64	89.15	E bank Mon-Fri[1]	57.34	61.13
E night	98.20	104.69	E bank Sat	71.90	76.65
F night	109.99	121.07	E bank nights	100.67	107.31
G night	125.09	125.27	E bank Sun	86.40	92.10
H night	132.89	133.14	E bank half	45.87	48.90
D half	49.51	50.94	E bank half Sat	57.52	61.32
E half	56.11	59.82	E bank half Sun	69.12	73.68
F half	62.85	69.18	E bank long day	95.98	101.88
G half	71.30	71.58	E bank long Sat	119.85	127.76

[1] 'Bank' indicates an internal hospital bank nursing system. The costs for these shift types were also derived for D grade bank nurses and D and E grades employed from external nursing agencies.

Appendix 6.4 Medical Staff Costs at LTH and DGH

1. LTH ICU

Financial year: 1994/95 (Costs include wages, London allowances and employer contributions):

i. Fifteen consultant sessions per week plus 2 sessions per weekend = 17 consultant sessions/week: £104 per session;

ii. 1 full time Senior registrar (mid grade, including 20 class 3 ADHs): £691 per week;

iii. 4 full time Senior house officers (mid grade, including 20 class 3 ADHs): £547 per week.

Total cost per annum: £241644

Total patient days per annum: 1830

Total cost per patient day (24 hours) stay: £132.

2. DGH ICU

Financial year: 1994/95 (Costs include wages, London allowances and employer contributions):

i. Fourteen consultant sessions per week plus 2 sessions per weekend = 16 consultant sessions/week: £104 per session;

ii. 1 whole time equivalent registrar (mid grade): £612 per week;

iii. 1 whole time equivalent senior house officer (mid grade): £547 per week.

Total cost per annum: £135980

Total patient days per annum: 1110

Total cost per patient day (24 hours) stay: £124.

Appendix 6.5 Derivation of Drug Costs at DGH and LTH

Non-drug overheads for the pharmacy departments were available from both centres. These were allocated to each drug dose, independent of the acquisition cost of the drug. Pharmacy overhead per original pack dispensed was derived by calculating the total number of drug items dispensed for the month of July, 1994 (a month in the middle of the study). The cost per original pack dispensed was £1.10 at LTH and £1.48 at DGH. One ampoule of drug used from a box of ten ampoules is given an overhead cost of £0.11 or £0.148.

The drug costs derived include the acquisition cost of the drug provided by the pharmacy department; the pharmacy overhead cost; the costs of disposables used in reconstitution (needles, fluids, syringes), disposables used in setting up and maintaining an infusion (infusion giving sets, intravenous fluids). These costs were obtained from contract prices and the NHS Supplies Catalogue November 1994 (North Thames Anglia Division). An example is illustrated below (LTH)

Fusidic acid 500mg iv

Drug acquisition cost	4.78
Pharmacy overhead cost	1.10
Sodium chloride 0.9% 500ml	0.67
Pharmacy overhead cost	0.11
Maintaining infusion (cost per dose)	0.29
Total cost per day:	£6.95 per dose + 0.79 per day (infusion setting up cost)

Appendix 6.6 Resource Use and Costs Associated with Monitoring and Interventions at LTH and DGH

The main areas of resource use are physiotherapy, respiratory and renal support, insertion and maintenance of vascular access and rental of special beds (LTH only). An example of the components of costs listed is provided.

Physiotherapy Costs

Physiotherapy constitutes the largest staff cost to ICU after nursing and medical staff. At LTH, the physiotherapy department record how many 15 minute of physiotherapist time are spent with each patient. Cost to the hospital of employing a physiotherapist for 15 minutes on ICU was reported as £7.00. At DGH, the physiotherapist recorded if she treated the patient only. Cost to the hospital was reported as £20.00 per session.

Cost of Respiratory Therapy

(Costs listed are those for interventions at LTH. These costs were also derived for DGH)

Blood gas measurement	0.19
Minitracheostomy	16.62
Oral intubation:	12.17
Percutaneous tracheostomy	123.51
Suction	0.87
Tracheostomy tube changes	16.74

Daily ventilation maintenance costs vary depending on type of ventilation used:	
Intubated (dry breathing system)	3.82
Intubated (wet breathing system)	13.40
Maintenance of tracheostomy	7.58
Intubated on CPAP	8.00
Self ventilating on CPAP	14.27
Self ventilating on oxygen mask	4.06
Cost of Insertion of Lines	
Arterial cannula	15.56
Epidural catheter	23.51
Nasogastric tube	4.98
Peripheral catheter	5.12
Pulmonary artery catheter	108.43
Quadruple lumen central intravenous catheter	42.24
Triple lumen central intravenous catheter	36.50
Urine catheter	6.87
Cost of Insertion of Drains	
Abdominal drain	16.98
Chest drain	18.59
Intracranial bolt	306.69
Cost of Renal Replacement (Continuous haemodialysis and haemofiltration)	
Insertion of bilumen 'vascath' catheter	43.34
Installation of dialysis filter and circuit	76.74
Dialysis fluid (pharmacy cost)	8.50
Replacement fluid (pharmacy cost)	8.50

Monitoring costs include ECGs, blood sugar tests, eye and mouth care. Other interventions include DC cardioversion, management of bradycardic arrest, rental of special beds, brain stem death tests and post mortem care.

Example of Components of Resource Use and Cost Associated with an ICU Intervention

Insertion of quadruple lumen central intravenous catheter (LTH):

Component	**Cost/£**
Quadruple lumen catheter	24.95
Sterile gloves	1.00
4 3-way taps	1.16
Tegaderm	0.40
Dressing pack	0.27
Scalpel (disposable)	0.16
Suture	8.69
Lignocaine 1% 10ml	0.43
Hepsal 2 vials	0.44
2 10ml syringe	0.08
3 needles	0.03
Sterile gown	1.15
Large sterile towel	0.26
Incopad	0.08
Single transducer	10.44
Total	**49.64**

Appendix 7.1 Derivation of Logit Regression Models to Explain ICU and Hospital Mortality at DGH and LTH

A7.1.1 Derivation of Logit Regression Model to Explain ICU Mortality at LTH

The development of a logit regression model to explain ICU mortality at LTH using patient admission characteristics is described in this section. All covariates investigated in individual analysis were included in a preliminary generalized logit model, Model A. Table A7.1.1 summarizes the logit regression analysis carried out on ICU mortality. PROC CATMOD within the SAS statistics package was used. The estimates of coefficients of covariates, their errors and individual significance are listed. If the coefficient estimate is not significant ($p > 0.05$), the covariate does not have a significant effect on mortality. Table A7.1.1 indicates that Model A approximates to a logistic distribution as the likelihood ratio test is non-significant. However, the presence of so many non-significant covariates ($p > 0.05$, so it cannot be excluded that the estimate of coefficient of covariate is zero) introduces uncertainty. The variation in the error terms of the nonsignificant covariates decreases the robustness of the model. The aim of this analysis is to derive a model with a significant intercept and estimates of coefficients, minimal interaction between covariates, whilst fitting a logistic distribution.

Table A7.1.2 summarizes the correlation between the covariates in Model A. Correlation between covariates exists for this data set ($n = 207$, 5 missing APACHE II scores) if the correlation coefficient (ρ) is greater than the critical value of 0.164 ($p < 0.01$). There is significant interaction between covariates. Some interaction is artefactual, such as the high correlation between surgical categories. Some correlation is

intuitively correct, such as the correlation between elective admissions and patients with cancer (due to the elective curative and palliative surgery carried out at this centre). Some correlation has probably occurred by chance, such as the negative correlation of surgical iatrogenic events with presence of cancer. Significantly correlating pairs investigated were: ELECT*CANCER; AGE*VASCULAR; AGE*GENERAL; VASCULAR*ELECT; NEURO*INFECT. These composite covariates were put back into a reduced logit model to assess their combined explanatory effect and to assess their correlation with other single covariates.

The first step was to remove non-significant, non-interacting covariates one by one and assess the impact on the model. For example, removal of the covariate SEX results in a loss of 3 degrees of freedom and a decrease of 2.43 in the maximum likelihood ratio (χ^2 distribution, $p>0.25$). Therefore, this reduced model is not significantly different from Model A. This approach was used to produce the 'best' model possible from the dataset, testing for interaction at each level.

Table A7.1 Logit Regression on Patient Admission Factors Explaining ICU Mortality (Analysis of Maximum Likelihood Estimates and Analysis of Variance) Generalized Model A

Source	Estimate	Standard	DF	χ^2	P
Intercept (β_0)	4.854	1.725	1	7.92	0.0049
Sex	0.118	0.202	1	0.34	0.5604
CANCER	-0.006	0.288	1	0.00	0.9838
CPR	0.533	0.354	1	2.26	0.1324
Age[1]	0.003	0.013	1	0.06	0.8118
APACHE II[1]	-0.141	0.035	1	16.38	0.0001
ELECT	-0.121	0.306	1	0.16	0.6921
VENT	0.242	0.286	1	0.72	0.3963
NEURO	0.125	0.287	1	0.19	0.6639
GENERAL	-0.203	0.317	1	0.41	0.5225
VASCULAR	-0.213	0.397	1	0.29	0.5908
TRAUMA	-0.882	0.608	1	2.10	0.1472
OTHER	-1.286	0.643	1	3.99	0.0456
IATRO	-0.090	0.299	1	0.09	0.7630
CHRONIC	-0.131	0.224	1	0.34	0.5592
CARDIAC	0.525	0.322	1	2.66	0.1027
INFECT	0.069	0.257	1	0.07	0.7894
Likelihood ratio	-	-	185	170.39	0.7720

[1] Continuous variables converted to categories to reduce number of populations

Table A7.1.2 Correlation Matrix of Covariates in Model A

1 Intercept	1.00															
2 Sex	0.14	1.00														
3 Cancer	0.07	-0.18	1.00													
4 CPR	-0.32	0.05	-0.13	1.00												
5 age	-0.55	-0.10	-0.11	-0.01	1.00											
6 APACHE	-0.36	-0.03	-0.07	0.11	-0.18	1.00										
7 elective	-0.06	0.07	-0.36	0.11	0.15	-0.12	1.00									
8 vent	-0.18	-0.05	0.03	-0.18	0.01	-0.00	0.01	1.00								
9 neuro	-0.44	-0.01	-0.02	0.09	0.16	-0.05	-0.01	-0.17	1.00							
10 general	-0.50	-0.04	-0.22	0.24	0.38	-0.13	0.03	-0.11	0.42	1.00						
11 vasc	-0.50	-0.19	0.24	0.14	0.35	-0.12	-0.30	-0.10	0.44	0.49	1.00					
12 other	-0.56	-0.08	-0.10	0.06	0.13	0.20	-0.01	0.12	0.20	0.27	0.23	1.00				
13 trauma	-0.50	-0.07	0.03	0.13	0.01	0.07	-0.01	-0.01	0.21	0.19	0.18	0.10	1.00			
14 iatro	0.06	0.09	-0.28	-0.17	0.05	-0.06	0.06	-0.11	-0.06	-0.20	-0.28	-0.19	-0.07	1.00		
15 chronic	0.03	-0.07	0.14	-0.10	0.20	0.03	-0.08	0.11	-0.03	-0.08	-0.08	-0.08	-0.01	0.05	1.00	
16 cardiac	-0.04	-0.05	0.10	-0.04	0.05	-0.15	-0.20	-0.01	0.03	-0.08	0.01	-0.13	-0.00	0.01	-0.24	1.00
17 infect	-0.28	0.15	-0.13	-0.03	0.13	0.22	0.26	0.08	0.30	-0.03	0.07	0.13	0.02	0.13	-0.15	-0.07	1.00
Source	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17

The most robust model derived from the dataset using the methods described is outlined in Table A7.1.3. The intercept and all covariates included are individually significant and there is no interaction between covariates. Model B also is not significantly different from Model A. This was shown by the likelihood ratio test. The loss of 182 degrees of freedom results in a drop of 165.66 in the likelihood ratio. The likelihood ratio has a χ^2 distribution, so its associated p-value is 0.70, indicating that the two models are not significantly different.

Table A7.1.3: Logit Regression on Patient Admission Factors Explaining ICU Mortality (Analysis of Maximum Likelihood Estimates and Analysis of Variance) Reduced Model B

Source	Estimate (β_n)	Standard error of β_n	DF	χ^2	Ψ [2]	P
Intercept (β_0)	-2.715	0.776	1	12.24	0.06	0.0005
CPR	0.757	0.321	1	5.55	2.13	0.0185
APACHE II[1] 16-18	0.580	0.278	1	4.35	1.79	0.0370
APACHE II 19-20	0.912	0.263	1	12.02	2.49	0.0005
APACHE II 21-30	1.096	0.240	1	20.94	2.99	<0.00005
APACHE II 31-44	1.571	0.600	1	6.96	4.81	0.0083
Likelihood ratio	-	-	3	4.73	-	0.1926

[1] Continuous variables converted to categories to reduce number of populations, categories compared with APACHE II score 0-15.

[2] Log odds ratio

The logit expression of Model B is expressed by the following equation:

$$\begin{aligned}\text{Logit (ICU mortality)} = \quad & -2.715 + 0.757(\text{CPR}) + \\ & 0.580(\text{APACHE 16-18}) + \\ & 0.912(\text{APACHE 19-20}) + \\ & 1.096(\text{APACHE 21-26}) + \\ & 1.571(\text{APACHE 27-44})\end{aligned}$$

The test of how well a logit model fits the data from which it is derived is to assess its sensitivity (correct prediction of death), specificity (correct prediction of survival), false positive rate (predicted to die, but lived) and overall correct prediction rate (see table A7.1.4).

Table A7.1.4 Fit of Logit Model B (Explanation of LTH ICU Mortality by Admission Characteristics) to Parent Dataset

Model Parameter	Results of running logit on parent dataset (%)
Sensitivity	100
Specificity	98.1
False positive rate	1.9[1]
Overall correct prediction rate	98.6

[1]Three patients who lived were predicted to die on the ICU.

A7.1.2 Logit Regression Analysis of Hospital Mortality at LTH

Model C was developed for explanation of hospital mortality, summarised in Table A7.1.5.

Table A7.1.5 Logit Regression on Factors Explaining Hospital Mortality (Reduced Model C)

Source	Estimate (β_n)	Standard error of β_n	DF	χ^2	Ψ^2	P
Intercept (β_0)	-4.898	0.893	1	30.06	0.01	<0.0005
PA catheter on ICU	0.517	0.198	1	6.82	1.68	0.0090
Neurosurgery	0.714	0.246	1	8.44	2.04	0.0037
CPR	0.950	0.454	1	4.37	1.57	0.0365
APACHE II[1] 16-18	0.679	0.227	1	8.90	1.97	0.0029
APACHE II 19-20	1.018	0.256	1	15.76	2.77	0.0001
APACHE II 21-26	1.483	0.423	1	12.28	4.41	0.0005
APACHE II 27-44	1.925	0.552	1	12.19	6.86	0.0005
Likelihood ratio	-	-	20	19.98	-	0.4591

[1] Continuous variables converted to categories to reduce number of populations, categories compared with APACHE II score 0-15.

[2] Log odds ratio

Table A7.1.6 Fit of Logit Model C (Explanation of LTH Hospital Mortality) to Parent Dataset

Model Parameter	Results of running logit on parent dataset (%)
Sensitivity	100.0
Specificity	95.3
False positive rate	4.7
Overall correct prediction rate	97.0

Although the covariate 'NEURO' was independently significant in Model C, removing it improved the 'fit' of the model so that specificity was 99.2% and overall correct prediction was 99.5%. Removal of any of the other covariates in Model C rendered the restricted logit model significantly different from the unrestricted model.

A7.1.3 Derivation of Logit Regression Model to Explain ICU Mortality at DGH

This section assesses to what extent the outcome of patients can be predicted on their admission to ICU at DGH. A correlation matrix was derived for all the covariates in the analysis. This detected the extent of two-dimensional interaction between the covariates. Marginally significant multicollinearity ($n = 137$, critical $\rho = 0.220$, $p = 0.05$) was detected between many combinations of covariates but none produced independently significant principal components. The resulting model D is summarised in Table A7.1.7.

Table A7.1.7 Logit Regression on Patient Admission Factors to Explain ICU Mortality at DGH (Reduced Model D)

Source	Estimate (β_n)	Standard error of β_n	DF	χ^2	Ψ^2	P
Intercept (β_0)	2.045	0.396	1	26.69	7.73	<0.00005
MEDICAL	1.280	0.397	1	10.38	3.60	0.0013
APACHE II score > 20[1]	0.776	0.298	1	6.77	2.17	0.0093
Likelihood ratio	-	-	1	0.01	-	0.9258

[1] Continuous variables converted to categories to reduce number of populations: category compared with APACHE II score 0 to 20.

[2] Log odds ratio

Table A7.1.8 Fit of Logit Model D (Explanation of DGH ICU Mortality) to Parent Dataset

Model Parameter	Results of running logit on parent dataset (%)
Sensitivity	100.0
Specificity	100.0
False positive rate	0.0
Overall correct prediction rate	100.0

A7.1.4 Derivation of Logit Regression Model to Explain Hospital Mortality at DGH

This section investigated which factors affect hospital mortality. The resultant model E is described in Table A7.1.9.

Table A7.1.9 Logit Regression on Factors to Explain Hospital Mortality (Reduced Model E)

Source	Estimate (β_n)	Standard error of β_n	DF	χ^2	Ψ	P
Intercept (β_0)	0.884	0.371	1	5.69	2.42	0.0171
ELECT	-0.603	0.279	1	4.66	0.55	0.0309
VENT	0.622	0.265	1	5.52	1.86	0.0188
APACHE II score >20[1]	0.495	0.237	1	4.37	1.64	0.0365
HOSPLOS > 6 days[2]	-0.554	0.259	1	4.58	0.57	0.0324
Likelihood ratio	-	-	9	13.98	-	0.1231

[1] Continuous variables converted to categories to reduce number of populations: category compared with APACHE II score 0-20.

[2] Continuous variables converted to categories to reduce number of populations: category compared with length of hospital stay of 0 to 6 days.

Table A7.1.10 Fit of Logit Model E (Explanation of DGH Hospital Mortality) to Parent Dataset

Model Parameter	Results of running logit on parent dataset (%)
Sensitivity	87.2
Specificity	100.0
False positive rate	0.0
Overall correct prediction rate	96.1

Appendix 7.2 Effect of Centre on ICU, Hospital and 6 Month Mortality: Logit models

Datasets from the two centres were merged. The LTH logit models were run on the combined dataset to assess the effect of centre on six month mortality.

A7.2.1 Logit Regression Analysis of 6 Month Mortality of the Two Centres

Model A1 was developed for explanation of 6 month mortality. The covariates summarised in Table A7.2.1 were found to retain independent significance.

Table A7.2.1 Analysis of Maximum Likelihood Estimates and Analysis of Variance (Reduced model A1)

Source	Estimate (β_n)	Standard error of β_n	DF	χ^2	Ψ [3]	P
Intercept (β_0)	-2.843	0.562	1	25.64	0.06	<0.00005
PA catheter on ICU	0.327	0.146	1	4.98	1.39	0.0256
Hospital LOS 6-11 days[1]	-1.015	0.278	1	13.34	0.33	0.0003
Hospital LOS >11 days	-1.300	0.229	1	32.22	0.27	<0.00005
Presence of cancer	0.636	0.170	1	13.99	2.89	0.0002
APACHE II[2] 16-18	0.574	0.206	1	7.79	1.77	0.0053
APACHE II 19-20	0.882	0.212	1	17.37	2.42	<0.00005
APACHE II 21-30	0.997	0.301	1	10.95	2.71	0.0009
APACHE II 31-44	1.244	0.252	1	24.31	3.47	<0.00005
LTH admission	0.272	0.148	1	3.38	1.31	0.0659
Likelihood ratio	-	-	57	76.84	-	0.0410

[1] Continuous variables converted to categories to reduce number of populations, categories compared with hospital LOS of less than 6 days.

[2] Continuous variables converted to categories to reduce number of populations, categories compared with APACHE II score 0-15.

[3] Log odds ratio

This model suggests that centre has a marginal effect on 6 month mortality. However, the model was significantly different from the unrestricted model. On investigation, it was found that when 'ELECT'

was controlled for, the centre lost significance. This model is summarised in Table A7.2.2.

Table A7.2.2 Reduced model A2 (Explanation of Six Month Mortality)

Source	Estimate (β_n)	Standard error of β_n	DF	χ^2	Ψ [3]	P
Intercept (β_0)	-2.297	0.585	1	15.40	0.10	0.0001
PA catheter on ICU	0.350	0.148	1	5.57	1.42	0.0183
Hospital LOS 6-11 days[1]	-0.944	0.280	1	11.37	0.39	0.0007
Hospital LOS >11 days	-1.199	0.228	1	27.75	0.30	<0.00005
Presence of cancer	0.735	0.173	1	17.97	2.08	<0.00005
APACHE II[2] 16-18	0.470	0.210	1	5.03	1.60	0.0250
APACHE II 19-20	0.749	0.217	1	11.87	2.11	0.0006
APACHE II 21-30	0.792	0.302	1	6.87	2.21	0.0087
APACHE II 31-44	1.058	0.250	1	17.98	2.88	<0.00005
ELECT	-0.471	0.158	1	8.89	0.62	0.0029
Likelihood ratio	-	-	48	59.24	-	0.1281

[1] Continuous variables converted to categories to reduce number of populations, categories compared with hospital LOS of less than 6 days.

[2] Continuous variables converted to categories to reduce number of populations, categories compared with APACHE II score 0-15.

[3] Log odds ratio

Table A7.2.3 Fit of Logit Model A2 (Explanation of 6 Month Mortality) to Parent Dataset

Model Parameter	Results of running logit on parent dataset (%)
Sensitivity	99.3
Specificity	97.7
False positive rate	2.3[1]
Overall correct prediction rate	98.5

[1] Four patients predicted to die within 6 months of discharge, who lived.