RATIONAL DECISION MAKING: AN APPLICATION OF DECISION ANALYSIS TO THE MANAGEMENT OF CHLAMYDIA TRACHOMATIS

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To
Mum & Dad

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Abstract

The term 'rational decision making' is used extensively in the arena of public policy-making, however little regard is paid to methodologies which can assist the decision maker. Complex decisions under conditions of uncertainty are made on an everyday basis, however this task can be simplified and the whole decision making process carried out in a logical and systematic manner by using decision analysis. Emphasis on more rational decision making, and in particular, rational prescribing has been a cornerstone of policy initiatives for governments. The task of the physician, in choosing an appropriate therapy becomes more difficult the more options that are available and, due to the inherent uncertainty involved in diagnosis of disease. Thus, decision analysis is applied to an area of public health importance, the management of infections caused by Chlamydia trachomatis. Chlamydia is one of the most common infections and when left untreated may lead to a substantial economic and social burden. The aim of this thesis is threefold: (1) evaluate the current economic burden attributed to Chlamydia, (2) to identify risk factors associated with *Chlamydia* infection, and (3) determine cost effective treatment options with the use of decision analysis. Suggestions for further research include (1) conducting similar studies on a national basis in order to assess the generalisability of results obtained from one GUM clinic in London (2) prospective collection of resource utilisation data in order to assess the real world clinical and cost-effectiveness of identifying individuals at risk for *Chlamydia,* and (3) evaluate cost-effectiveness of treatment for patients with a presumptive diagnosis of *Chlamydia*.

Chapter One

Introduction

Economics is concerned with the allocation of scarce resources whereas health economics aims to provide a systematic structure and methods for allocating resources specifically within the arena of public health. Health economics provides a wide range of methodologies, which may be used to assist decision-makers in the allocation of resources. The most widely methods used in Economic evaluations include cost minimisation analysis (CMA), cost effectiveness analysis (CEA), cost utility analysis (CUA) and cost benefit analysis (CBA).

Critics of the NHS have long argued that funding for the NHS always has and continues to remain insufficient, whilst advocates of government policies claim that expenditure on the NHS has increased, in real terms. However, the costs of healthcare are estimated to escalate both over the short term and the longer term. The most widely quoted reasons for the expected increase in healthcare costs are improvements in technology, development of expensive medical techniques, availability of new drugs, improvements in life expectancy and higher patient expectations. Under these conditions, it will be imperative to allocate resources efficiently. From an economic perspective, regardless of the actual amount of money allocated to the NHS there will always remain a need to allocate limited resources efficiently amongst the competing health interventions. Thus, health economic considerations provide policy makers with a wealth of information to allocate resources to those health interventions that represent demonstrable economic and clinical effectiveness.

The public health and economic importance of allocating resources to those health interventions which are both cost effective and clinically effective is now being

tackled in the UK through a recently created government body, the National Institute of Clinical Excellence (NICE). The remit of NICE is to provide guidance on the clinical management of patients including the use of health interventions such as pharmaceuticals and medical devices.

Drug costs account for approximately 11% of total NHS costs. However, despite this relatively low percentage, government policies during recent years have targeted drug costs as an area of cost containment. Measures to contain costs of prescribing include the setting up of drug formularies, automated prescribing software such as PRODIGY. More recently, the task of the reviewing body, National Institute of Clinical Excellence incorporates an evaluation of, and recommendations for the use of high volume or expensive drugs. To date, NICE has reviewed Relenza™ for the treatment of influenza and recommended that this drug should not be available on the NHS. Other reviews of pharmaceuticals during the year 2000 include treatments for Alzheimer's disease, Multiple sclerosis and treatment for Arthritis.

Antibiotics represent one of the most widely prescribed classes of drugs. The prescribing of antibiotics is particularly important from an economic perspective. Inappropriate prescribing of antibiotics and failure to comply with treatment may result in the development of resistant organisms. Such resistant infections cannot be treated with standard antibiotics, but require the use of more potent and often expensive antibiotics. In extreme cases where the infection is resistant to the most effective antibiotics currently available, infection may result in increased mortality. Indeed, a number of resistant infections such as tuberculosis which had been eradicated with the development of antibiotics in the 1940's are now returning in many countries. The management of *Chlamydia* trachomatis is particularly difficult due to the clinical nature of the infection. The vast majority of infections remain asymptomatic in individuals and

lead to a variety of issues. Firstly, asymptomatic infections that remain untreated can lead to the development of costly complications such as pelvic inflammatory disease (PID) and infertility. In addition, asymptomatic infections are more likely to result in transmission to sexual partners.

The aim of this thesis is threefold: (1) to identify the current economic burden of infections caused by *Chlamydia trachomatis* in women, (2) to identify risk factors associated with *Chlamydia trachomatis*, and (3) to identify cost-effective treatment strategies in the management of these infections.

The term 'rational' is often used in relation to the prescribing of drugs, particularly to the prescribing of antibiotics. Thus, chapter two will begin by presenting the reader with a basic foundation in the arguments and issues surrounding rational prescribing. An economic definition of rational prescribing is outlined in terms of *Homo economicus*. Rational man is shown to allocate resources according to economic efficiency. Factors resulting in an inefficient allocation of resources will be identified and discussed along with pertinent economic concepts of marginal costs and the production possibility frontier. Subsequently, the importance of rational prescribing in a clinical context will be outlined. A number of important factors when making a rational decision are identified and discussed. These include a discussion of the initial presentation of patient with symptoms, the subsequent clinical diagnosis, followed by choice of therapy, if any, the effectiveness of therapy and finally, communicating this information to the patient.

Having outlined both the clinical and economic perspectives on rational decision making, chapter three will present the theoretical basis of one methodology which has been used to aid rational decision making, the theory of decision analysis. This chapter is separated into three main sections: methods for modelling the decision

problem in a systematic and logical manner; methods to model levels of uncertainty in the decision problem including an assessment of individual decision-makers risk preferences; and methods to measure levels of utility associated with each decision path. A broad framework will require structuring the specific decision problem, often with the aid of graphical tools such as influence diagrams or decision trees. The final analysis produced identifies cost effective methods of achieving the desired outcomes.

Decision analysis, which originated from operations research has been utilised in a broad range of disciplines and in the last few decades has been increasingly applied to heath care. Thus, chapter four will outline methods of applying decision analysis, specifically within healthcare. Decision analysis can be used in the treatment of individual patients in a clinical setting or, in the analysis of treatment for particular groups of patients. A commonly used outcome of interest in the evaluation of healthcare interventions is the expected life of the patient. This is an appropriate measure of outcome since the objective of healthcare intervention is to prolong life through the eradication or alleviation of symptoms/disease. Life expectancy may be defined as the average length of time a person is likely to survive. Different states of health are measured using various types of measurement scales. In general, scales are rated between 0 for the lowest value and one, for the highest value, in order to incorporates these values into a decision analysis. Markov models are used in decision analysis in order to describe complex decision problems involving transitions into various states of health. There are two types of Markov models, Markov chains and Markov processes. The main disadvantages of using decision analysis relate to specific tools. In particular, scales that purport to measure health states are based on the premise that these states of health are easy to identify, clearly segregated and are quantifiable. However, the currently available scales do not meet all these criteria. As a

consequence, there is little consensus on the use of scales to measure health status both with generic scales and with disease specific scales.

Having outlined the theoretical framework for this thesis, chapter five represents a shift in focus towards an important public health issue requiring the attention of health economics, the management of *Chlamydia*. In order to facilitate the application of health economics and specifically decision analysis to the management of *Chlamydia*, chapter five provides the reader with a review of the clinical and the economic literature on *Chlamydia*. *Chlamydia* has been referred to as the 'silent epidemic' of the modern age and is the most common sexually transmitted infection (STI) in many industrialised countries including England, Wales and the U.S[1]. From a public health perspective, it is the sequelae of *Chlamydia,* which are important. In particular, *Chlamydia* is the leading cause of Pelvic Inflammatory Disease in England and Wales (CDR, 1998). *Chlamydia* trachomatis infection is the most common bacterial sexually transmitted disease in many industrialised countries and is the most economically significant infection after HIV. The main features of this infection are threefold; infection is often asymptomatic, sequelae may be severe and if left untreated, infection can persist for more than a year. The second half of this chapter will focus the reader's attention on the economic aspects of the management of *Chlamydia*. Studies on the economic burden of *Chlamydia* have not been conducted in the UK, however a review of a landmark study conducted in the U.S will be reviewed. Screening strategies for asymptomatic individuals in a broad range of sub-groups has been advocated. The cost effectiveness of such policies will be reviewed and discussed. Once patients have been diagnosed, treatment is available in the form of a wide range

[1] www.aomc.org/*Chlamydia*.html referenced on 14th Sept. 1999

of antibiotics. The cost effectiveness of different drug treatments is reviewed and discussed.

Having presented the reader with a clinical and economic overview of the management of *Chlamydia trachomatis*, chapter six presents empirical research on the economic burden of *Chlamydia* in England & Wales. Estimates of the economic burden of *Chlamydia* in the U.S and other industrialised countries suggest the infection represents a significant societal burden. Similar studies have not been conducted in the UK; the best estimates for the UK place the total economic burden of *Chlamydia* and its sequelae at approximately £50M per annum however these estimates are not based on systematic research. The methodology used to evaluate the economic burden of *Chlamydia trachomatis* and its sequelae is a prevalence-based cost of illness approach. The research evaluates the direct and indirect costs associated with the management of *Chlamydia* in primary care, secondary care and specialist genitourinary medicine clinics.

The significant economic burden of *Chlamydia* and its sequelae, as illustrated in chapter six, underscores the public health and economic importance of managing this infection appropriately. Whilst screening of asymptomatic individuals has been advocated as a potential method for reducing the costs associated with *Chlamydia*, universal screening of individuals is not a cost-effective alternative, thus there is a clear need for the identification of criteria for selecting patients who should be screened. Chapter seven presents the reader with an empirical study which aims to identify risk factors associated with *Chlamydia.* Data obtained from patients presenting to a genitourinary medicine clinic at St George's hospital, London is used to develop an econometric model to assess the significance of behavioural, demographic and clinical signs or symptoms of *Chlamydia trachomatis*.

Cost-effective treatment should be initiated only after asymptomatic individuals have been diagnosed through the use of appropriate screening tests. A variety of antibiotic treatments exist for the management of *Chlamydia*. Whilst economic evaluations of their use has been conducted in a number of countries including the U.S and Canada, limited research has been conducted in the U.K. Thus, chapter eight presents a decision analytic model to evaluate the cost effectiveness of antibiotic treatment in the UK setting. Finally, conclusions and recommendations to the management of *Chlamydia* are presented in chapter nine.

Chapter Two

Rational Prescribing

The term 'rational' is often used in relation to prescribing of drugs, particularly in the case of antibacterials. So, what is rational prescribing? How this question is addressed depends very much on who asks the question. This chapter will begin by presenting the reader with a basic foundation in the arguments and issues surrounding rational prescribing. A number of different perspectives for defining rational prescribing will be presented.

Firstly, an economic definition of rational prescribing is outlined in terms of *Homo economicus* in section 2-1. The assumption of global rationality underlies the ability of rational man to allocate resources according to the principles of economic efficiency in an environment where individuals have full access to perfect information or knowledge. The concepts of marginal costs and the production possibility curve are outlined. Finally, the factors resulting in an inefficient allocation of resources will be identified and discussed. Section 2-2 will outline the importance of rational prescribing in a clinical context. Clinicians do not have access to perfect information at the time of making clinical decisions therefore 'bounded rationality' is assumed to apply. Section 2-3 provides an overview of the policy implications for encouraging rational prescribing. Such methods include the use of selected lists, prescriptions charges, indicative prescribing amounts and education of both patients and prescribers.

Section 2-1

Rational Prescribing: an economist's perspective

2-1.1 Definition

The term 'rational prescribing' is often used in the medical and economic literature of health care, however a precise definition has yet to be outlined. According to the Oxford English Dictionary a person may be described as rational if: 'exercising one's reason in a proper manner; having sound judgement; sensible, sane' (OED; 1988:1740). Additionally, 'derived from, reason or reasoning; sensible; not foolish, or absurd' (OED; 1988:p.1740). Clearly, the emphasis is placed upon the ability to make a systematically and logically consistent decision. Indeed, the foundations of Economics are based upon the assumption of 'rational' consumers and decision-makers.

The Collins Dictionary of Economics (1988:p141) refers to 'economic man' as: 'an assumption in economic theory that individuals act rationally in specifying their objectives and then take decisions which are consistent with those objectives.'

However, it may be argued that the objectives of one individual from a purely subjective point of view may be rational, although another individual may regard the setting of these objectives as irrational. Moreover, although it is possible to set objectives in a rational manner, it does not necessarily mean that all objectives are indeed rational. Thus, it is not sufficient to state that the achievement of objectives in a rational manner is sufficient to satisfy the requirements of rational behaviour.

2-1.2 Rational Consumer

According to neo-classical demand theory, a rational consumer is defined as one who 'attempts to obtain the greatest possible satisfaction from the money resources they

have available.' (Collins; 1988:91). Rational consumer choice is easily defined using an illustration of indifference curves.

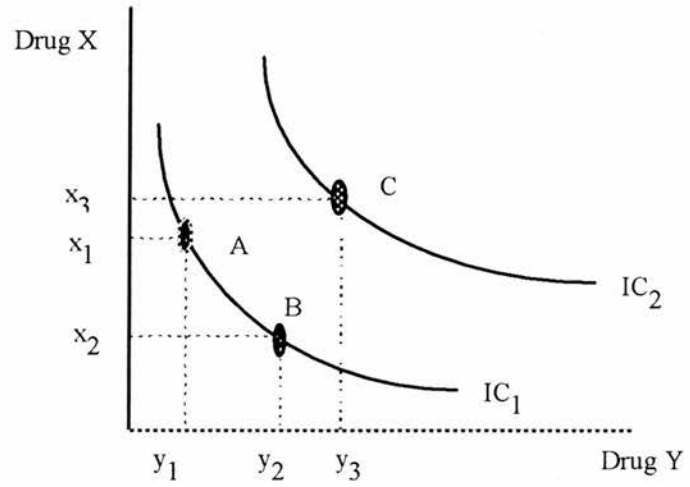

Figure 2.1: a set of indifference curves

Indifference curves show, as the name implies, an individual's preference for goods. An indifference curve effectively joins together all points where an individual is indifferent between the combination of goods chosen i.e. the level of utility obtained is the same at each point on the indifference curve.

In figure 2.1, the vertical axis measures the quantity of a good, drug X and the horizontal axis measures the quantity of another good, drug Y. Every point on the graph represents some combination of drugs X and Y, with lower quantities shown by points close to the origin; the further away from the origin, the larger the quantities of drugs X and Y. Points A and B are on the same indifference curve and therefore represent the same level of utility for the individual irrespective of the combination of drugs X and Y. However, point C is on a higher indifference curve than A and B representing greater quantities of both drugs, thus point C will be preferred to points A or B.

An assumption is made on the ability of the consumer to rank preferences such that any possible combination of drugs, X and Y can be considered and a choice made regarding preference or indifference for each combination of goods. Hence, an infinite number of indifference curves can be drawn to produce a map of indifference curves.

A rational consumer must be able to satisfy the following conditions: (a) rank preferences, (b) transitive behaviour and (c) demand is not infinite i.e. more of at least one good is always desired. From this, the properties of indifference curves for rational consumers may be deduced: (a) indifference curves never intersect, (b) shape is always downward sloping from left to right and (c) convex to the origin. Indifference curves represent marginal rate of substitution of one good for another whilst leaving the individual with the same level of utility.

However, indifference curves on their own do not tell us much about consumers choices, simply show his/her preferences. Additionally, information of levels of income and the price of the two goods must be available. The consumer will choose the combination of goods that will yield the highest level of utility i.e. the highest indifference curve.

A straight line showing the combination of goods that can be purchased, given a fixed level of income represents income. The point of intersection with indifference curves shows the consumer equilibrium point where the individual maximises his/her utility subject to income limitations. If consumer's income increases, the income constraint line will shift upwards, remaining parallel to the original line. Conversely, if income falls, the line will shift downwards and to the left. Further, if a change in the price of drugs occurs, the slope of the income constraint line will shift e.g. if the price of drug X increases, income line will shift downwards to the left, reflecting the lower

quantity that can be bought. Line pivots, and will not be horizontal to the original position.

2-1.3 Allocative efficiency

Just as individuals are thought to allocate their resources effectively, the goal of any economic system is the achievement of allocative efficiency such that all resources are fully utilised. No one individual can be made better off without someone else being made worse off. In order for allocative efficiency to hold, three conditions must be satisfied: (a) economic efficiency, (b) consumer efficiency and (c) equality of marginal social cost and marginal social benefit.

2-1.3 (a) economic efficiency

Economic efficiency is achieved when the cost of producing a given output is minimised. This entails producing the maximum number of outputs from given inputs and is referred to as technological efficiency (in addition, to using inputs at minimal cost levels). Further economic efficiency is attained whenever firms maximise profits hence perfect competition is economically efficient.

2-1.3 (b) Consumer efficiency

Similarly, consumer efficiency is achieved when individual cannot reallocate resources in such a way as to improve on initial allocation of resources. Thus, allocation of resources is maximised and can be shown in a demand curve. Each point on the demand curve will represent the quantity demanded at a given price when the individual has made the best possible use of his/her resources (income). Hence, if the quantity bought is a point on the demand curve, the consumer is said to have reached allocative efficiency.

2-1.3 (c) Marginal social costs and benefits

Thirdly, marginal social cost must equal marginal social benefit. Marginal social costs represent the costs of producing one additional unit of output and includes the costs borne by someone other than the producer (external costs) such as pollution. Marginal social benefits represent the monetary value from one additional unit of consumption including benefits to people other than the buyer (external benefits).

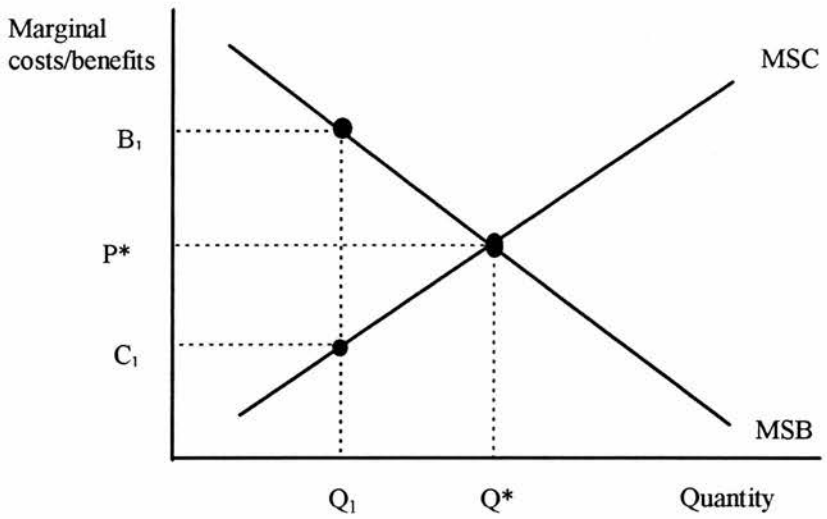

Figure 2.2: Efficient allocation of Resources

Allocative efficiency is defined as the optimal use of scarce resources in order to produce a combination of goods and services which meets the demand requirements of consumers. In a perfectly competitive market, allocative efficiency is achieved when no resources are wasted (there are no external costs or benefits). If output is Q_1, the marginal social cost is less than the marginal social benefit (B_1) therefore allocative efficiency is not achieved. Essentially, the MSC represents the industry supply curve, and MSB represents industry demand curve; allocative efficiency is achieved where price is P* and quantity Q*. It is now not possible to make one person better off without making another person worse off. In order to demonstrate that it is now not

possible to improve the welfare of one more person, consider restricting output to Q_1. Here, the marginal social cost is C_1 and marginal social benefit is B_1. At this point, consumers are willing to pay a higher price than C_1 upto a maximum of price B. At the same time producers are willing to supply more goods for a price higher than C. Thus, consumers and producers are able to gain by trading until they reach P* Q* at which point it is not possible for any one to gain without loss to another. The marginal benefit of the last unit consumed equals the benefit of the last unit produced for the supplier.

However, this situation can only occur when there are no external costs and benefits. It is only under these circumstances that the MSC is the supply curve in industry and MSB is the demand curve.

2-1.4 Production Possibility Curves

Inherent in the decision making process is the need to make trade-offs. For example, if the production of medical goods and services is increased through training more people to become health professionals, then fewer resources (and people) are available to produce other, non-health goods. Thus, a society has to make trade-offs between the quantity and quality of goods produced in an economy either explicitly (e.g. fixing quotas for professions, licensing etc.) or implicitly (principles of demand and supply). Allocative efficiency of goods is achieved when the optimal combination of goods and services is chosen reflecting society's preferences.

Additionally, the quantity of health care resources used is an important factor in the production of goods. Often, goods can be produced using many different combinations of inputs. For example, services in primary care can use either labour intensive techniques or capital intensive techniques. A high doctor patient ratio will reflect a labour intensive method whereas use of a large amount of technology relative

to number of patients is indicative of a capital-intensive method for servicing the same health needs. The goal of production efficiency is to ensure the best use of scarce resources by choosing the optimal mix of inputs for the production of each health service.

Productive efficiency is achieved when a health economy is producing services at any point on the production possibility curve. However, allocative efficiency is achieved when society chooses the most preferred point of production (again, along the PPC). This in turn will depend upon the value society places on the production of these services.

2-1.5 Inefficient allocation of resources

A number of problems arise to prevent an efficient allocation of resources. Problems arise when free competition is not allowed in the market place. Barriers to entry, the existence of external costs/benefits and monopoly power, all act to hinder an efficient allocation of resources.

2-1.5 (a) external costs and benefits

The existence of such costs and benefits results in an inefficient allocation of resources for the production of some goods. For example, some consumers who spend additional money on national defence will generate benefits for the whole society. If such products are left to the free market, the level of output will be too small to meet demand. Where external costs are created, the free market would result in an over-production of goods, as the producer is able to off-load some costs to others. Thus, the role of government is to provide a framework in which to encourage production of all goods with efficient allocation of resources.

Adam Smith, the founding father of Economics invented the principle of the 'invisible hand' which guides the behaviour of consumers and producers in order to produce the best possible social outcome. Inherent in this view is the achievement of allocative efficiency.

2-1.5 (b) Barriers to entry

Government license is used to control the number and type of producers. For example, a license is needed to practice law, medicine and dentistry. Additionally, it is not possible to set up business in particular industries without a license e.g. broadcasting on radio and television requires a government license. Since 1842, there has been a government law in the UK pertaining to issue of patents. These are granted in order to provide exclusive rights to the inventor of a product or service for a limited period of time. In the UK patents are granted for 16 years (Parkin & King:1992:p296). The idea behind the granting of patents is to protect the inventor from other producers who can easily duplicate the good or services without having incurred the costs of invention.

2-1.5 (c) Monopoly

Allocative inefficiency exists under monopoly market conditions when output is reduced to below a competitive level in order to attain artificially high prices and consequently higher profits. The fundamental problem in economics is the utilisation of given and scarce resources. The premise is based upon the notions of unlimited demand for health goods, which cannot be met through limited and scarce resources. Hence, society must choose to allocate scarce resources in such a way as to maximise benefits of production. This question can best be illustrated with the aid of a simple diagram.

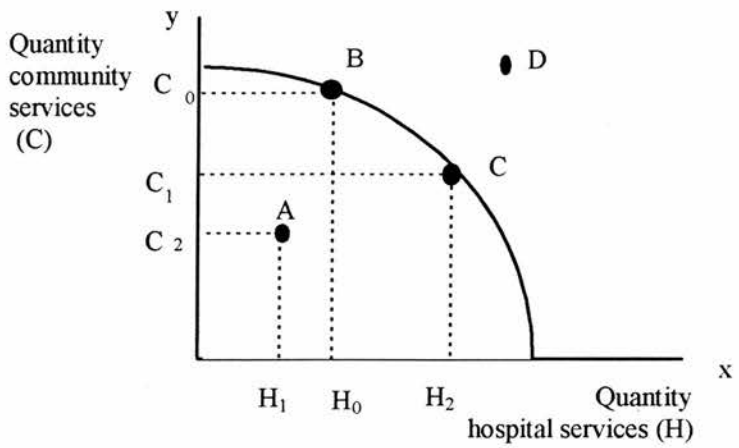

Figure 2.3 Production possibility curve for quantity of Hospital and Community services

The quantity of community, C and hospital, H, services are shown on the x and y axis, respectively. Assuming that health care resources are scarce at any given point in time, and level of technology is also fixed, then the curved line shows the combinations of community and hospital services that can be produced efficiently in a health economy. Every point on the line depicts full utilisation of given resources. However point A shows an under-utilisation of given resources and point D represents a level of production which is outside the scope of limited resources; this level may be attained of either the level of resources is increased or technology levels improve to make production more efficient. Hence, the existing PPF will shift and pass through the point D.

Assume health economy is at point B on the production possibility frontier with C_0 and H_0 combination of community and hospital services. However, if a new point, C is chosen as the preferred combination of services to produce; the movement from point B to point C on the curve reflects that C_0 - C_1 units of community care have to be given up in order to produce additional units of hospital care of H_2 - H_0. Thus, in order to produce additional units of hospital care, some units of community care must be given up; the forgone units of community care represent the opportunity cost of

producing additional units of hospital care. The shape of the curve displays the law of increasing opportunity cost. Increasingly more units of one good must be given up in order to obtain successively more units of another good.

2-1.6 Summary of section

This section has provided definitions of rational decision-makers and the process by which rational decision-making is achieved. The key assumption that underlies rational decision making from the perspective of economics is that of the availability of perfect information and global rationality. Consumers and decision-makers are assumed to maximise their potential gains within cost constraints. In addition, just as consumers make a trade-off in the type of goods purchased, society must trade-off allocation of resources for production of health goods. Productive efficiency is achieved when a health economy is producing services at any point on the production possibility curve; allocative efficiency is achieved when society chooses the most preferred level of production, given societal values.

Section 2-2

Rational Prescribing: a clinical perspective

2-2.1 Definition

Rational prescribing in a clinical context requires a qualitative analysis of the patient's condition. Rational decision making based on global rationality cannot exist in a clinical context, as perfect information is not available to clinicians. Instead, a bounded version of rationality may be applied, where clinicians act in a rational manner based on the limited available evidence. Within the constraints of bounded rationality, Marinker & Reilly (1994) list five necessary components for placing rational prescribing in the context of a rational clinical process: (a) diagnosis, (b) clarity of therapeutic intention, (c) data on effectiveness of drugs, (d) communication with the patient, and (e) follow-up

2-2.2 Diagnosis

According to Balint (1964) a major characteristic of the doctor's work is the 'organisation of unorganised illness'. This is usually carried out at one of two levels, symptoms or pathology. The first method requires an analysis of the symptoms, the second method requires the use of laboratory evidence, or inferred from patient history and probability values published in the medical literature. The role of a specialist on the other hand is to minimise uncertainty and error while the role of the GP is to accept levels of uncertainty and minimise side-effects. Thus, a rational choice for treatment is made only when the diagnosis is established through exploring the probability of disease. It is only under these circumstances that a level of uncertainty in the diagnosis is acceptable and the therapy chosen reflects rational prescribing. An additional role of

the GP is to provide therapy not only for the physical well-being of the patient but also for social and psychological aspects. Prescribing treatment may reflect the latter.

2-2.3 Therapeutic intention

Therapy can be prescribed for a number of reasons; to eliminate a disease (e.g. antibiotic for a bacterial infection), relief of symptoms (e.g. use of pain-killers) or to help limit effects of a chronic illness (e.g. inhalers in treatment of asthma). However, unless the level of diagnosis is clear, the intention of therapy may not be easily identifiable.

A common feature of general practice is diagnosis at the level of symptoms. Marinker & Reilly (1994) use an example of diagnosis in the case of a patient presenting with lethargy and no other symptoms. A blood test may reveal anaemia, however the doctor makes an initial diagnosis of iron deficiency and prescribes the relevant vitamin. Thus, the prescription will cure the symptoms without curing the anaemia. However, if the patient does not respond to the iron, the doctor will need to look for more evidence to identify the chronic disease, where anaemia is only one aspect. Thus, the response to treatment may help to identify the cause of disease.

2-2.4 Efficacy of therapy

There is an inherent bias in the provision of data relating to pharmaceutical products by the relevant stakeholders. Endorsing specialists and pharmaceutical companies are interested in their own commercial success and personal reputations. Equally biased is the government and associated bodies. Their ultimate duty is to provide an efficient health service, however this must be achieved within certain cost constraints.

Another source of potential error is the ability of the GP to diagnose across almost the whole range of clinical conditions for all types of patients. It is virtually impossible for the GP to be an expert in such a wide range of conditions and the thousands of treatments available. Thus, the majority of GPs work with a much more limited range of drugs, an estimated 300; the problem with national and often regional formularies is that each doctors personal list of 300 drugs is likely to be very different to other doctors (Marinker: 1994). The government has suggested the need for a framework into which information about drugs could be provided (Audit Commission: 1994). Such a framework should include the following:

Figure 2.4: Information components for rational prescribing

1.	Class, generic name, and proprietary name of drugs
2.	Therapeutic actions
3.	Levels of side-effects and interactions with other drugs
4.	Indications and contra-indications
5.	Recommended doses and regimes
6.	Costs
7.	Significant differences from previously established drugs in the same class, or drugs with an almost identical therapeutic intention
8.	Risk-benefit analysis
9.	Cost-benefit analysis

Source: Marinker & Reilly;1994:p.99

As financial constraints are imposed on all healthcare systems, the use of health economics in assessing the economic costs and benefits of treatments will play an increasingly important role in rational prescribing. The availability of such information will enable the doctor to make an informed decision on a rational choice of treatment.

2-2.4 Communication with the patient

An important aspect of general practice is the need to communicate the rationale for choice of therapy. The diagnosis made by the doctor will depend on epidemiological research; cause and effect based on laboratory/clinical experiments. However, the patient may also have views on the likely cause of illness and appropriate choice of therapy.

The doctor must be able to communicate the risks of both relative and absolute levels of risk. In the area of preventative health care, the patient will need to understand that the disadvantages of taking medication now can prevent a serious illness in the future. However, if this is not fully understood, or accepted by the patient then compliance to treatment will be low. Additional information, which must be conveyed to the patient, includes timing and dosage of medication and dietary advice. Since the average consulting time in the UK is only 10 minutes, it may not be possible to convey the process of rational prescribing to the patient.

2-2.5 Follow-up

Finally, the doctor will often ensure follow-up of a patient to monitor progress of a chronic illness. A system of repeat prescriptions has been devised to ensure re-call of patients for assessment where medication is long-term. An additional factor in follow-up consultations is to check for compliance to therapy and possible side-effects. In the case of acute illness, a follow-up may simply consist of the patient making a call to the surgery to confirm eradication of symptoms.

2-2.6 Summary of section

Determining rational prescribing is a complex issue; indeed it is easier to define what constitutes bad practice than to define elements of good clinical practice. However, rational prescribing in a rational clinical context can be separated into a number of different categories. Initial diagnosis of symptoms based on probabilities for disease; choice of appropriate therapy based on efficacy of treatment and associated side-effects; communicating information about disease and therapy to patient in order to maximise compliance; follow-up of patient to monitor progress and compliance.

Section 2-3

Policy implications of rational prescribing

2-3.1 Measures to Control Costs of Prescribing

Everyone recognises the funds available to spend on drugs are limited, and it is therefore up to prescribers to ensure that the very best use is made of these funds. As medical knowledge advances and new drugs are introduced, GPs have increasing opportunities to prescribe for the real benefit of their patients. Unfortunately, increased prescribing opportunities usually lead to increased costs: ACE inhibitors for heart failure, corticosteriods for asthma and safer anti-depressants provide significant benefits at a price. There is a danger that in the current climate of budgetary restraint, these advances will be the ones that come under most pressure. It is therefore very important that prescribing is as rational and cost-effective as possible (Prescriber May 1994 editorial p.9)

2-3.2 Prescription Charges

The most consistent policy to simultaneously control costs and curb demand has been the use of prescription charges. The effect of such a policy has been a reduction in the average number of prescription items received by patients eligible for prescription charges. However, this effect may be ameliorated by the tendency of some doctors to prescribe larger quantities of drugs per item. In the case of antibiotics however, this is unlikely to be the case, as these drugs are not usually prescribed in large quantities, as there would not be any clinical benefits. Nevertheless, the success of a policy of prescription charges is constrained by the number of people who are eligible for exemptions to prescription charges (elderly, children, low income etc.) who represent

approximately half of the population. In addition, high consumers of drugs often purchase exemption certificates thereby waiving prescription charges for a small fee. Only 14% of prescriptions are actually paid for, therefore drastically limiting the potential for reducing costs of treatment and unnecessary prescribing.

2-.3.3 Selected Lists

A selected list has been in place since 1994. The purpose of this list is to limit the type of drugs doctors are allowed to prescribe. In general, more of the expensive brand drugs may not be prescribed on the NHS. Although, there was a one-off savings in drug expenditures it does not appear to have halted the increase in drug expenditure.

2-3.4 Indicative Prescribing Amounts (IPAs)

Indicative prescribing amounts are set by FHSAs in consultation with doctors. Monthly reports are then sent to each practice by the PPA to show levels of expenditure in relation to the initial budget set. Again there is little evidence to show if this policy has helped to contain costs of drugs. Prescribing budgets for GPs are set according to the basic cost of drugs and do not take into account pharmacist's professional fees. Budgets are set differently for fundholding doctors and do not apply to other doctors. Indicative prescribing Scheme was introduced in 1990 whereby all practices are set a financial target within which prescribing costs are meant to be limited. If for any reason the targets are exceeded, an explanation/case must be made to the FHSA through an intermediary such as medical or pharmaceutical adviser. The IPB is based on the Net Ingredient Costs (NIC) of drugs. This is the price the government has agreed to pay pharmacists for the drugs as listed in the Drug Tariff. PACT data quotes NIC of drugs.

Fundholders can reduce prescribing costs simply by prescribing fewer items. 'This occurs because container allowances and discounts are based on the number of items. An item means a single item on an FP10 and is not related to the duration of treatment for that drug. Thus three separate prescriptions for one month's supply of a drug will incur three container allowances and increase the apparent volume in the calculation of the discount. However, the same treatment issued as one prescription for three months' worth of treatment will incur only one container allowance and reduce the discount amount deducted from the budget.' (Prescriber, 19 July 1994 p:47) Thus, providing an incentive for fundholders to reduce the number of items prescribed by increasing the length of time for which a prescription is issued. However, longer length prescriptions will increase the potential for wastage of drugs if patient requires a change of therapy or indeed the patient moves away to another practice (more frequent in urban areas) which would represent unnecessary expenditure for the fundholder. For non-fundholding GPs, prescription length has no net impact on the prescribing budget, although a move to increased length of prescription will reduce the number of items and increase the average cost per item in direct proportion. Some FHSA's and their advisers see a lower number of items and a higher average cost per item as indicative of 'good prescribing'.

2-3.5 Education

Although the science of prescribing, pharmacology and applied therapeutics is taught at medical schools; the art of prescribing, formulating a therapy strategy by choosing the appropriate treatment regimen, explaining risks and benefits of therapy, compliance to therapy and assessing the outcome of therapy is left out. Thus, junior doctors and trainee GPs, will not have the experience of practised doctors in the art of prescribing.

The contrast between the relatively short time spent on these topics in medical education and the dominant role that prescribing plays in practice is remarkable (Marinker & Reilly:1994). Furthermore, factors affecting prescribing: sales and marketing techniques of pharmaceutical companies, patient expectations and demand, expert opinion, peer pressure and adult learning theory and limitations of budgets are not subjects traditionally taught in medical schools. Although, as there is greater involvement of the medical profession involvement in managing e.g. National Health Service trusts and GP fundholders, budgetary controls will become an increasing popular subject. Information and advice on rational prescribing is sent out to GPs in the form of bulletins (BNF, Drug and Therapeutics bulletin, ABPI data sheet compendium etc.) More importantly, the Prescription Pricing Authority in the form of Prescription and Cost analysis (PACT) provides data to each doctor on a quarterly basis. Since the mid 1980's, general practitioners in England have received prescription analysis and cost reports (PACT data); similar reports are available for doctors in Scotland, Wales and Northern Ireland. Information on the volume and cost of prescribing is detailed for each practice and compared to local and national averages. Further, information on current issues is provided. However, only those areas of clinical practice where cost are a major concern. Rational prescribing or inappropriate prescribing, is not limited to expensive drugs. Additional details of prescribing are sent to those doctors who are expensive prescribers. Any doctor requiring more detailed information on his/her prescribing patterns can also request such information. The effects of such a policy are difficult to assess, however, it can be assumed that education of prescribers should lead to more appropriate use of treatments. However, this may not necessarily coincide with attempts to reduce costs of the drug bill. Each FHSA appoints a medical and pharmaceutical advisor who acts

as a liaison officer between the authority and the practice. One of the many roles of such advisers is to set targets for fundholding GPs. Medical audit advisory groups (MAAG) also play an important role in educational programmes aimed at improving rational prescribing.

2-.3.6 Promoting Rational Prescribing

The problem of irrational prescribing is endemic. It has been documented to occur in a number of different ways, prescribing of expensive drugs that are not proven to be cost-effective, incorrect use of antibiotics (Till, B. 1991), and polypharmacy, prescribing drugs not related to the diagnosis (Wheedle, 1991; Goodburn, 1989).

The International Network for Rational Use of Drugs (INRUD) and the WHO Action Programme on Essential Drugs have developed and tested a set of indicators to measure rational prescribing. These key indicators are identified in table 2.5.

Table 2.5 Indicators for prescribing

Prescribing Indicators
1. Average number of drugs per encounter
2. Percentage of drugs prescribed by generic name
3. Percentage of encounters with an antibiotic prescribed
4. Percentage of encounters with an injection prescribed
4. Percentage of drugs prescribed from essential drugs list or formulary

Source: WHO/DAP/93:1

However, in order to evaluate rational prescribing, a standard of reference is required. Agreed standards can only exist if there is a consensus of opinion on the practice of medicine and of prescribing.

2-3.7 Impact of controls

Studies have attempted to evaluate the use of selected policies on levels of prescribing. Avorn and colleagues (1983) demonstrate education through printed matter has little influence over prescribing behaviour. The underlying assumption used is that prescribers can improve their prescribing by simply improving their knowledge i.e. lack of knowledge leads to poor prescribing *ipso facto* improved knowledge will lead to improved prescribing. However, other variables such as patient demand, effects of advertising, intentional use of placebo drug and personal preference of doctor are important determinants of prescribing behaviour. Additionally, it is the irrational prescribers who are least likely to read educational material posted to them and thus do not gain any benefits (Hogerzeil, 1994).

More influential methods of improving Prescriber behaviour include the use of treatment guidelines, structured prescription forms and face-to face educational campaigns. Grimshaw & Russel (1993) carried out a systematic review of 49 published evaluations on the effects of guidelines demonstrates a marked improvement in the care of patients.

In order to maximise benefits of essential drug lists and guidelines, these should be accompanied by sustained promotional campaigns. Further, physicians. should be encouraged to participate in drawing up these recommendations.

2-3.8 Training of future prescribers

Medical schools place emphasis on learning the science of medicine, however, little time is spent on the art of medicine. Students are taught to accumulate medical knowledge rather than techniques of problem solving and that of rational decision making on choosing an appropriate course of treatment (Nierenberg, 1986). Indeed, training from undergraduate level needs to place more emphasis on the practical needs

of the future Prescriber (Hogerzeil, 1994). Studies should be designed to help the individual student to evaluate different treatment strategies. Secondly, training in the clinical stage also needs to be improved. Teaching hospitals have traditionally placed much more emphasis on a correct diagnosis and relatively little time is spent on choosing the appropriate course of therapy. Where guidelines exist, students should be taught the rationale behind the development of the guidelines.

Thus, medical students should have a thorough understanding of the concepts of rational prescribing by the end of their undergraduate courses. Further, clinical training should be used to emphasise the practical aspects of rational prescribing. The widespread use of formularies or hospital guidelines for antibiotic therapy in UK hospitals is an encouraging sign (Working part of the British Society of Antimicrobial Chemotherapy, 1994) in the continuing battle against irrational prescribing. Policies aim to encourage the use of older drugs with proven efficacy rates, where costs are often far below that of new antibiotics. Antibiotic costs are also increased greatly through the use of intravenous drugs, often 10-times more expensive than oral antibiotics (Davey & Nathwani). Additional costs incurred when antibiotics are administered through the intravenous route include additional time of qualified staff and other equipment.

Stocks of drugs held in chemists should be limited, thereby allowing the pharmacist the opportunity to negotiate better prices for block contracts, whilst increasing the turnover of drugs thereby cutting out wasteful stocks. Inappropriate prescribing of drugs can expose patients to unnecessary risks of side-effects. Ponge et. al. (1989) showed approximately 26% of hospitalised patients suffering from adverse effects were prescribed the initial therapy inappropriately. Further, environmental factors should also be considered where antibiotic treatment is prescribed unnecessarily

potentially leading to an increase in the selection of drug resistant bacteria. Inappropriate or irrational prescribing increases the costs of care without adding any benefits. Davey & Nathwani advocate using hospital antibiotic policies as a priority for promoting rational prescribing. Similar policies are recommended for general practice (Wyatt et. al. 1990).

Davey & Nathwani recommend that results of implementing antibiotic policies should be monitored through audit. These results should, if necessary and appropriate, lead to changes in antibiotic policies. Thus, a two-way flow of information is seen to be vital for the promotion of rational prescribing.

Table 2.6 List methods for implementing antibiotic policies

Target	**Strategy**	**Outcome**
Education		
Reduce use of specific drug	mailed info	transient effect, unsuccessful
Substitute specific drugs	drug bulletin	successful
Compliance with formulary	formulary, no feed-back	unsuccessful
Persuasive strategies		
Reduction in costs of iv antibiotics	feedback of costs to individual with peer comparison	unsuccessful
Promote use of cheaper alternatives	educational advertising campaign with poster	Success
Improve dosing	structured educational order form	Successful
Reduction in iv Antib costs	cost info added to microbiology form	Successful
Reduction in iv antib costs	guidelines for switching from iv to oral dosing	Successful

Source: Davey & Nathwani, 1998

There are limited data to demonstrate rates of efficacy for different implementation strategies. Nevertheless, the least successful method has been educational information in the form of printed matter. The most effective strategy has been face -to-face

presentations. This has long been the cornerstone of advertising in the pharmaceutical industry (Cockburn et. al. 1992).

The developers of the policies are a key to the success of their implementation (Grimshaw & Russel, 1994). They recommend the developers should consist of senior clinicians as well as external public health officials in order to maximise compliance with policies. Thus, in the case of general practice, a committee of GPs should develop guidelines in conjunction with local and then national policy makers. It is recommended that initially, each practice should develop guidelines of antibiotic policies appropriate to its population and then move onto local and finally national guidelines. An alternative method would be to begin with national and finally arrive at individual practice level guidelines. Finally, it is important to provide information to prescribers on the level of compliance with guidelines and to provide data on the overall effects of such prescribing on patient care as well as the drug budget for the individual practice or hospital.

Compliance can be enforced through dictatorial policies of re-imbursement for a limited list of drugs only. Thus, penalise those doctors and patients in whom a drug not listed in the formulary is genuinely required, however such methods are unlikely to provide long term benefits and may lead to medicine becoming a static science. Instead, the educational method of compliance is urged.

Monitoring policies is yet another important area. Auditing is facilitated through the use of advanced information systems, however, such systems are not vital. Indeed, the process of auditing is itself an educational process and should be seen as a valuable learning opportunity (Davey & Nathwani1998).

Recommendations should include type of therapy, drug dosage, length of duration and the route of administrations. Implementation of antibiotic policies have

been shown to decrease the costs of health care in general practice (Panton, 1993). Policy effects on resolving levels of resistance and in development of resistance. It is very difficult to prove this. In fact, there is little evidence to demonstrate policies prevent the spread of resistance as there are a host of other variables, which lead to increased resistance. Nevertheless, policies help to improve the quality of prescribing thus eliminating irrational prescribing.

2-3.9 Future of prescribing

The complexity of the tasks undertaken by doctors has been outlined. Given that demand for health care is rising and the supply of health care products continues to increase, the full responsibility for prescribing of drugs may not lie with the GP. Indeed, it has been suggested that the clinical task may be desegregated in the future (Marinker & Reilly). The main task of the GP would be to determine the diagnosis, and the therapeutic strategy. However choosing the specific drugs may be left to a practice pharmacist. The pharmacist would be responsible for choosing the exact drug, dosage and to communicate this information to the patient. Further, monitoring of the patient would be left to joint responsibilities of the practice nurse and pharmacist.

However, management of prescribing in this way is likely to be met with resistance from the medical professions. Although, changes in medical technology have been accepted as advancement of science, the notions that similar advances in the structure of the medical profession has not been accepted. One of the main objections to the treatment of patients in this group way is the emphasis placed upon the personal relationship between a patient and doctor. The structure and function of primary care teams would be radically changed. Such changes are already taking place in the USA where managed care has opened the way for pharmacy benefit management (PBMS).

These companies are developing disease management protocols, development and management of drug formularies, prescription processing and management of compliance. If similar changes do start to take place in the UK, fundamental principles of general practice will be challenged. The greatest fears revolve around the patient fitting into a treatment protocol rather than a treatment being fitted to suit the patient.

2-3.10 Summary of section

This chapter has focused on the term 'rational prescribing'. It has been shown that the interpretation of this widely used term depends very much on the perspective of the user. Thus, a clinician's view of rational may not necessarily coincide with that of an economist, nor the government. A number of potential variables affecting prescribing behaviour were proposed and tested with empirical work. This research showed a large number of variables have contributed to the increase in levels of prescribing for antibiotics. Inevitably, this has caused an increase in the total drug bill for the NHS. Respiratory infections were identified as the single largest, although not the only cause of an increase in antibiotic prescriptions. Patient factors, which have had an impact on prescribing, include an increase in the average consumption per patient. This is re-enforced with an upward trend in the number of consultations for respiratory conditions. Doctors also seem to be prescribing for a larger proportion of patients. However, one of the drawbacks of this study is the inability to distinguish between different severity of disease. Underlying such patterns of utilisation are a series of factors: Ageing population, wider range of conditions can be treated, patient education has led to increased demand, increased resistance to antibiotics and changing patterns in the NHS e.g. shift from secondary to primary care services. Although, levels and

costs of prescribing antibiotics have increased, there is limited evidence to suggest that doctors are not prescribing rationally.

Section 2-4

Summary of chapter two

This chapter has provided an overview of the differing perspectives on rational decision making, specifically focusing on rational prescribing. Attempting to define the meaning of the term *rational* is indeed a difficult task. The interpretation of this work depends very much on the context within which it is used. Thus, for an economist, *rational* is synonymous with *Homo Economicus* with an underlying assumption of global rationality. Where consumers (the decision makers) maximise their utility given the cost constraints, given access to perfect information. Trade-offs between different types of goods are made using a utility function. In medicine, the assumption of global rationality is difficult to apply since decision makers often have to work on the basis of extremely limited information, therefore an assumption of bounded rationality is used whereby decision makers act rationally, given limited information. It is often easier to define irrational prescribing, nevertheless, a rational diagnosis of a patient entails diagnosing a disease using published (as well as subjective) assessments on the probability of the disease. Choice of therapy should be based on proven efficacy of treatment regimens. The information must be communicated to the patient, and followed up in order to maximise compliance with treatment.

Chapter Three

Theory of Decision Analysis in Healthcare

The previous chapter provided an overview of the contexts within which rational decisions are taken. This chapter will aim to provide the reader with an overview of one specific methodology, which can aid rational decision making, the theory of decision analysis.

The theory of decision making is concerned with how decisions should or ought to be made. As such it is a matter of concern to almost everyone, either as someone who has to make decisions or, as a person who has to implement decisions made by others. Many decisions made on an everyday basis are often trivial, for example a decision whether to drink a pint of lager, or a pint of beer is unlikely to have major consequences. However, a decision regarding the choice of subjects to be studied at university is likely to have more important consequences. Decision analysis is a 'prescriptive approach designed for normally intelligent people who want to think hard and systematically about some important real problem' (Keeney & Raiffa; 1976: p.vii).

It is often said that making good decisions in medicine is an art rather than a science (Weinstein & Fineberg:1980) however, it can, like science, be learned in a systematic and methodological manner. Medical students are able to learn the science of medicine through the learning of facts and theories, the art of evaluating and treating patients through experience, but they receive little training for systematic methods of making decisions for the treatment of individual patients. The role of the physician is to make decisions on behalf of each individual patient; should the patient be treated; or, should the physician wait until further diagnostic information becomes available. These are the types of questions physicians are faced with on a daily basis.

Some of the decision problems will be fairly routine whilst others will be of a more complex nature with a great deal of uncertainty surrounding the situation and thus require considerable amount of thought before arriving at a decision. The purpose of clinical decision analysis is to complement and enhance clinical judgement; it is not intended to replace the experience of physicians. Decision analysis can be used in the treatment of individual patients in a clinical setting or, as has been the case more recently, in the analysis of treatment for particular groups of patients, thus addressing policy issues (Pettiti, 1995).

Section 3-1 will briefly outline the history of and a definition of decision analysis. The theory of decision analysis is separated into three main sections. Section 3.2 presents methods for modelling the problem in a systematic and logical manner. Section 3.3 outlines the uncertainties in decision making and methods for estimating probability values. Section 3.4 will discuss individual utility functions and methods for evaluating utility of health. A summary of the chapter is presented in section 3.5

Section 3-1

A Brief History And Definition Of Decision Analysis

3-1.1 History of Decision Analysis

The discipline of decision analysis is a derivative of operations research and game theory. There exists both Classical Decision Analysis and Bayesian Decision Analysis. Abraham Wald wrote the first complete work on Classical Decision Analysis in 1950. Scholars such as Raiffa, Savage and Schlaiffer, forming a new field of Bayesian Decision Theory further developed the work. By the mid 1940's, decision analysis was applied to a wide range of economic issues according to the principle of maximising expected utility (Von Neumann & Morgenstern: 1944). However, applications of decision analysis in medicine did not take place until the following decade. In 1959, Science published an article by Ledley & Lusted 'Reasoning foundations of Medical Diagnosis: Symbolic logic, probability, and value theory aid our understanding of how physicians reason ' on the theory of decision analysis. The first published article on an application of decision analysis in medicine in 1967 looked at the surgical procedure of radical neck dissection in patients with oral cancer (Henschke & Flehinger1967). Decision analysis attracted further attention, following the publication of articles by Lusted (1971) and Kassirer (1976) which demonstrated the applications of Decision Theory in medicine (Petitti: 1994). From then on, the use of decision analysis in medicine grew at a fairly steady pace through the 1970's and in 1981 a journal titled 'Medical Decision Making' began publication.

3-1.2 Definition of Decision Analysis

Decision analysis is a methodology providing a logical and systematic process for structuring and solving complex decision problems (Raiffa: 1968; Lindley: 1971, Weinstein & Fineberg: 1980, Pettiti: 1995). The approach is explicit forcing decision-makers to structure the problem, to identify the various components, uncertain variables and possible outcomes. The prescriptive approach is designed to convey and accept that humans are not perfect decision makers and can make better decisions with the guidance and structuring offered by decision analysis (Clemen, 1991). It is designed to act as an aid to decision makers and describes what they should do under a given set of circumstances; Decision analysis does not aim to model the thought process of the decision-maker who does not use this methodology. Psychological studies of the thought processes of physicians provide a useful lesson on the advantages and disadvantages of decision analysis (Dawes: 1988; Elstein et. al.: 1978)

There are five main steps in decision analysis. The first step involves identifying the components of a decision problem; options available to the decision-maker, uncertain events and the possible outcomes of these uncertain events. The second step of decision analysis requires a logical and systematic structuring of the decision problem with the use of tools such as influence diagrams and decision trees. Thirdly, estimation of probability values. Fourthly, the decision tree or influence diagrams are solved. Finally, a sensitivity analysis is carried out in order to test the assumptions of the model. Depending on the results of the sensitivity analysis, the decision model may be adjusted.

Section 3-2

Modelling the decision problem

This section will address the issue of modelling decision problems, a fundamental part of the decision analysis process. The basic elements of modelling decision problems includes the identification of the various components consisting of available options, uncertain events and the outcomes of these uncertain events (Raiffa: 1968; Lindley: 1971; Weinstein: 1980; Clemen: 1991) Section 3-2.1 will demonstrate the use of influence diagrams and decision trees as representations of the decision problem. Both tools are especially useful for developing the structure of complex problems in a simple graphical format. In addition, decision trees display a more detailed, and alternative graphical representation of the decision problem. Section 3-2.2 will show how to solve both, decision trees and influence diagrams with the use of the concept of expected monetary value (EMV).

3-2.1 Components of Decision Problems

The first step in structuring a complex decision problem is that of identifying the various components which make up the decision problem (Clemen: 1991). These components consist of (a) available options, (b) uncertain events, and (c) outcomes. This section will look at each of these components and where possible illustrate with the use of examples.

3-2.1(a) Available Options

Whenever an individual is faced with a decision, s/he must choose between two or more options. The decision whether to drink a pint of lager or beer is that of two alternative actions which may be taken. Often, the decision situation will involve a series of decisions that must be made at each step of the process. For example, a

biotechnology company must decide which of the many thousand chemical products discovered in its laboratories should be developed further. Having made a decision, the next problem that arises is whether or not a patent license should be purchased. A further sequential decision would be whether to test the new chemical entity (NCE) in a small sample of patients or perhaps to sell the product to a pharmaceutical company. The decision-maker will need to consider all the options at each stage. Whenever the immediate decision problem is to be solved, the decision-maker must consider the decision prior to the present one, and all subsequent decision problems at the outset of attempting to solve the initial decision problem. Graphically, decisions are shown as a series of squares (figure 3.1).

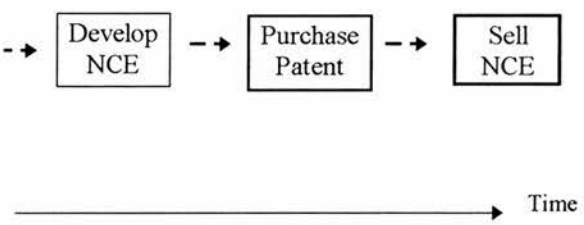

Figure 3.1 A series of decision problems

It is important that all possible choices are presented in the decision problem; it is therefore inadequate to simply include a decision and the negation of that decision as an alternative (Clemen, 1991). To return to our earlier decision problem, it would not be sufficient to consider the option to drink a pint of lager, or not to drink a pint of lager. A decision-maker must consider all viable alternatives. In this example the decision problem would be whether drink a pint of lager, a pint of beer, or indeed, to have a drink at all.

At the outset of decision making it is imperative that all possible choices of actions be identified and listed. The list should be both exhaustive and mutually exclusive (Raiffa, 1968). Decision analysis can only be applied to those options, which are included in the specific problem thus, if a further option exists but is not included in the list, and subsequent analyses will not be able to take account of this option. Although it may sometimes be possible to be certain that all reasonable alternatives have been included, one cannot be certain that a viable option has not been excluded. In fact the success of many entrepreneurs in business relied on the individual originating an alternative action rather than choosing from existing options. However, Decision Analysis is not concerned with theories of how to develop innovative actions but rather, to concentrate on using a logical and systematic method for choosing from an exhaustive list of reasonable and possible actions. In addition, the decisions are both exclusive and exhaustive:

'...one of them has to be taken, and at most one of then can be taken. Alternatively, they exhaust the possibilities, and the choice of any one excludes the choice of any other' (Lindley: 1971:6).

3-2.1(b) Uncertain Events

Decision problems are made more complex due to lack of information about the future. An investment in the stock exchange is a classic example where the shareholder is uncertain as to what will happen to the price of the shares. Factors affecting the price of shares may include the company performance relative to its competitors as well as overall economic performance. Uncertainty is the main reason a decision can become complex. In many decision situations there will exist a series of uncertain events; the larger the number of these uncertain events the more complex the decision situation becomes. Furthermore, each uncertain event may depend on a previous

uncertain event and is likely to have an effect on subsequent uncertain events. By convention, uncertain events are represented by circles (figure 3.2).

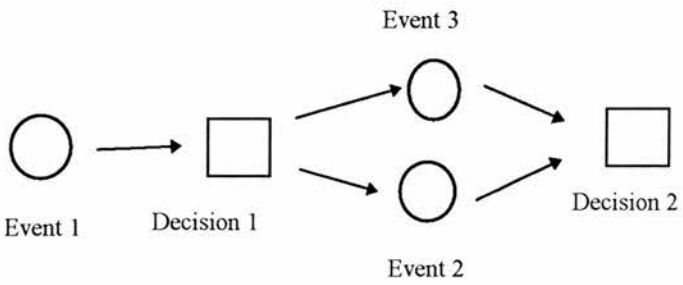

Figure 3.2 a series of uncertain events

An arrow from a group of uncertain events to a decision indicates that the outcomes of the events are known at the time of making the decision. The uncertain events are linked to the various decisions in a time sequential manner. The order in which the uncertain events occur may or may not have a natural order. If the former is the case, then modelling this natural order of uncertain events in a logical manner may help the decision-maker. However, it is far more important for the uncertain events to be linked to each decision stage in terms of the available information, rather than the order in which the uncertain events occur (Clemen, 1991).

3-2.1(c) Outcomes

The outcome of the decision problem is the final result once all the uncertain events are resolved and the decision(s) taken. The outcome is measured in a unit appropriate to the analysis. In the case of the biotechnology company, and the stock market investor, the outcome of interest may be profit. In a clinical situation the outcome of interest may be the eradication of an illness, or the results of a test.

An important issue which must be resolved by the decision-maker at the start of the problem is that of identifying an appropriate time horizon, at the end of which the outcome of the decision problem may be analysed. Thus, the stock market investor must decide how far into the future the investment must be made. The biotechnology company must decide its time horizon for obtaining a profit. The doctor must decide whether the time horizon should include the length of the patients' life or until the end of that particular episode of illness. In an ideal situation, one would wish to look as far ahead into the future as possible, however, one must balance planning into the future with the practical aspects of implementing decisions.

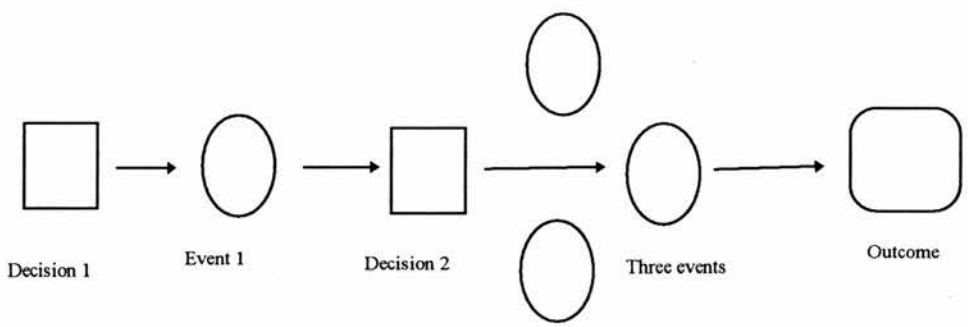

Figure 3.3 Final addition of an outcome

3-2.2 Structuring decision problems

The second stage of the decision process involves structuring of the components identified in the first stage into a logical and temporal sequence. Here, the stage at which a decision must be made and the availability of additional clinical information is clearly identified. It is important to incorporate time within this structure in order to identify the events and information that precede any one decision node. Then the outcomes for each decision path and the associated possible events are specified within the structure. The method of structuring may be in the form of either an influence

diagram or in the shape of a decision tree. The advantages of using decision analysis include the ability to be able to model in a logical and structured manner through the use of tools which aid this process; this section will describe the use of two such tools: influence diagrams and decision trees.

3-2.2 (a) Influence Diagrams

An influence diagram is a graphical representation of the decision problem. Different shapes represent the various components of the decision problem. As a standard in decision theory, decisions are represented by squares, oval shapes represent uncertain events and outcomes are represented by rectangles with rounded corners. Arrows then show the relationships between the components. Each shape is usually referred to as a node, whilst the arrows are referred to as arcs. A node at the start of an arc is known as a predecessor, and a node at the end of the arc is a successor. The rules for using arcs to represent relationships among nodes are as follows:

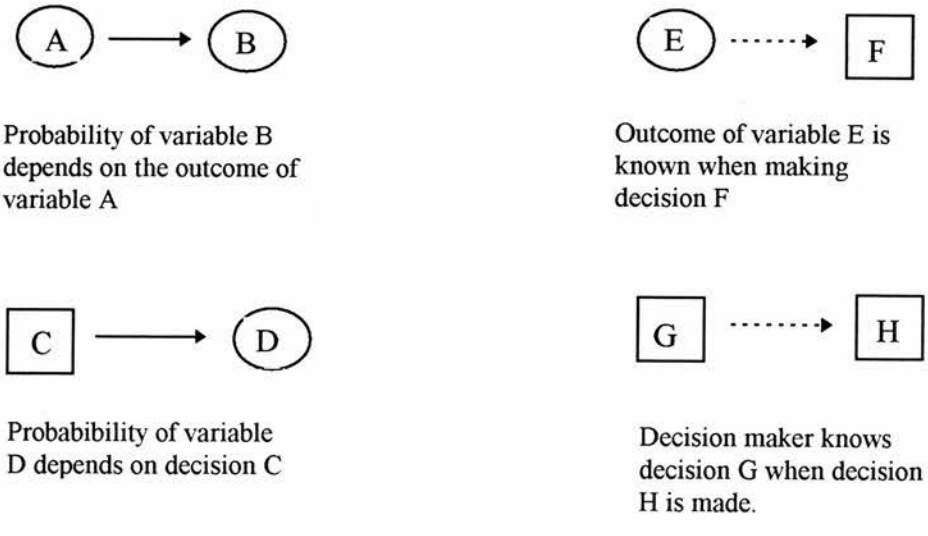

Figure 3.4 Rules governing relationships between arcs in Influence Diagrams
Source: Howard & Matheson, 1980.

All decision and chance nodes will precede the value node, as the final outcome is dependent on both the decision and the chance event. Also, there is no need to place an arc between the decision and the chance nodes, since at the time the decision is made, the decision-maker does not know whether the project is likely to succeed or to fail. In general, solid lines represent relevance of a node and broken lines represent available information. An influence diagram that has been correctly structured will not have a cycle; there is no way of following arrows from A to B to C, and then to repeat the process in reverse. Once, a particular node has been left, it is not possible to return to the starting point.

Consider a simple decision problem, where the decision-maker chooses one option, where there is one uncertain event and an outcome. As an example, consider again the biotechnology company that must decide which chemical product it should continue to invest in. If a further investment is made, the product is likely to prove either a success or a failure. If the company decides not to invest in a particular chemical product, it may choose to invest in a different product or it may decide to sell the product to a pharmaceutical company (see figure 3.5).

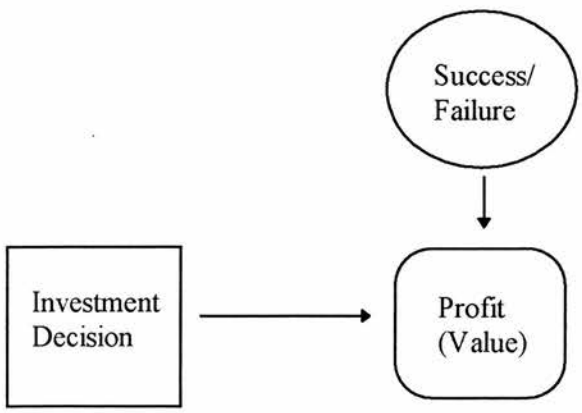

Figure 3.5 an investment decision for a biotechnology company

A correct form for the construction of influence diagrams does not exist with the exception of the conventions of symbols and arcs. However, the decision-maker should aim for a requisite model. A model is said to be requisite if it depicts all the relevant components of the problem (Clemen, 1991). The best strategy for developing a requisite model is to start off with a very simple influence diagram and then add other aspects of the decision problem as and when, they become necessary.

A number of common mistakes are often encountered in the construction and analysis of influence diagrams. Firstly, influence diagrams are often confused with flow charts. An influence diagram is not simply a sequential representation of a series of decisions and events; instead it depicts a decision situation at a point in time where all the relevant uncertain events (chance nodes) are taken into account on making a decision. Chance nodes represent the possible events that may take place reflecting the level of uncertainty in the decision-maker's mind. Secondly, again linked to the confusion of influence diagrams with flow charts, is that of placing arcs between chance nodes and the decision node. The general idea is to reflect the level of uncertainty in existence at the time of making the decision unfortunately such arcs actually represent the complete opposite i.e. the outcome of the uncertain events is thought to be known and is usually not the case. A third mistake often encountered is that of attempts to make the influence diagram circular. An influence diagram is simply used to help structure the decision problem at a point in time and cannot represent a circular flow of events.

3-2.2 (b) Decision trees

Although influence diagrams are very useful for providing a basic structure to a decision problem, often a more detailed description of the problem needs to be displayed. A more appropriate tool in such instances is that of using a decision tree.

Here again, the same rules in terms of symbols apply, such that decisions are represented by square, uncertain events by chance nodes and outcomes by a value node (see figure 3.6).

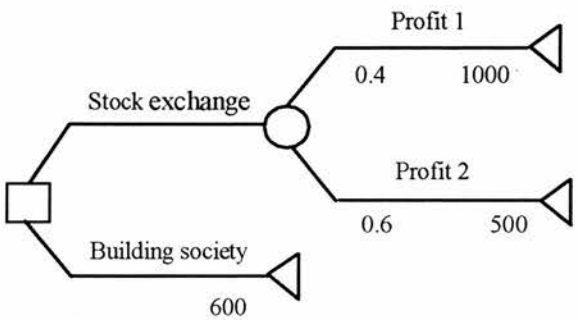

Figure 3.6 A decision tree with two options

The available options, which emanate from a square, are two alternative options such that only one alternative may be chosen. For example, for a decision-maker to choose between an investment in the stock market or a building society, s/he may choose only one option. Branches emanating from chance nodes must represent mutually exclusive and collectively exhaustive outcomes. In other words, only one outcome can occur and no other outcomes are possible. It may be useful to consider the decision tree as showing a decision problem in a chronological manner; starting on the left-hand side, a decision is made followed by subsequent chance events or further decisions.

One of the most commonly used methods to choose from among a number of risky alternatives is to use the concept of Expected Monetary Values (EMV). Calculating the EMV for decision trees is otherwise known as 'folding back' the tree. Starting on the right hand side of the tree, the process involves calculating expected values for chance nodes. For example, the expected value for the alternative to invest in the stock market is calculated as follows:

$$(0.4 * 1000) + (0.6*500) = 700$$

The expected value for option to invest in building society = 600 (certain value, no risk is involved). Since the EMV for the decision to invest in the stock exchange is higher than the alternative to investment in a building society, the former alternative should be chosen.

Although, EMV is simple to use there may be decision problems where the use of EMV is not a sufficient criteria with which to choose an alternative; this problem will be discussed in section 3 of this chapter.

3-2.2 (c) Foliating the decision tree

A decision tree can include as many alternatives, chance events and outcomes as the decision-maker may wish to include. However, it is important to simplify the decision tree to include only those variables, which are of maximum importance in actually making a decision. The more complex a decision tree becomes, the more difficult it is to think clearly and concisely about the immediate decision problem. In fact, the art of decision analysis includes the ability to know when to simplify a problem, and when to make the problem more complex. The opposite of simplifying the decision tree is known as 'foliating' (Raiffa, 1968; Bunn, 1984; Clemen, 1991). This involves going back to a simplified model of the decision problem and looking at a particular area of interest in more detail.

The advantages of a reduced form of the tree include the ability to simplify the identification of the best strategy in a complicated decision problem. Furthermore, the reduced form specifies the extent to which the optimal course of action is dependent upon the underlying probabilities related to each chance node. A subsequent advantage

is the ease with which this facilitates sensitivity analysis for the assessment of probabilities.

The amount of imperfect information available to the decision-maker is shown in the various stages of the decision tree. A problem arises when a decision-maker is forced to choose between two options, where at least one of the outcomes of each decision path is a desired objective of the decision-maker.

Decision trees certainly show much more information compared to influence diagrams, however this can become a disadvantage when the problem is so complex that the tree becomes very large and therefore more difficult to interpret. Influence diagrams on the other hand are able to represent very complex problems in a simple form, which is easily understood and does not require the use of any mathematical techniques. For the decision-maker, influence diagrams are a useful method in which to begin structuring the problem. Once more information becomes available or more detail needs to be added to the problem, the decision-maker should then convert the influence diagram into a decision tree. The two tools are said to be isomorphic such that a correctly structured influence diagram may be converted into a decision-tree and vice versa. Thus, these tools should be seen as complementary rather than separate tools.

Section 3-3

Modelling uncertainty

The preceding section has demonstrated the role of uncertainty in decision making; here techniques for assessing and measuring levels of uncertainty will be outlined. Section 3.3.1 will provide a brief introduction to the theory of probability. Subjective probability assessment forms an important part of decision analysis, methods to asses such probability values with the use of theoretical probability models will be outlined in Section 3.3.3. In many situations, however, levels of uncertainty may be similar to a standard situation, where the uncertainty may be modelled with the use of a standard mathematical model will be discussed in section 3.3.3. The final section will discuss the use of Monte Carlo Simulation as a method to create data, which may then be used in the assessment of probability values.

3-3.1 Theory of Probability

Attempts at a formal definition of probability have been made since the 17th century, with a continuous debate between mathematicians and philosophers. However, the most widely accepted definition relies on the mathematical definition. The probability of an event occurring is the relative frequency of the event taking place in a number of observed and independent trials (Gray, J.R: 1967).

The underlying theory of probability is relatively simple and is based on three premises. If X and Y are any two events, the axioms are as follows:

(a) $p(X \mid I) \geq 0$

where I represents present state of information.

(b) $p(X) \text{ or } p(Y) = p(X) + p(Y)$

If X and Y are mutually exclusive events, the probability that either X or Y is the sum of their individual probabilities.

(c) $p(X,Y) = p(E_1)\, p(E_2)$

If X and Y are independent variables, the multiplication axiom states that the probability of both X and Y is the product of their individual probabilities.

3-3.1(a) Joint, Marginal and Conditional Probabilities

Uncertainty of decision problems is rarely satisfied by a set of mutually exclusive and collectively exhaustive events. A more common description of uncertain events will rely on the use of join, marginal or conditional probabilities.

If X and Y are any two events, the joint probability for the two events occurring is $p(X,Y|I)$. The marginal probabilities are obtained by summing joint probabilities across rows or columns. Conditional probabilities are defined from joint and marginal probabilities. If X and Y are any two events, then $p(X|Y, I)$ is the conditional probability (probability X occurs, given that Y occurs and state of information, I). The conditional probabilities may be calculated using the following formula:

$$p(X|Y, I) = \frac{p(X,Y|I)}{p(Y|I)}$$

3-3.1 (b) Bayes' Rule

This is a relatively simple rule to relate conditional and marginal probabilities. Bayes' theorem plays an important role in decision analysis. Given two sets of mutually exclusive and collectively exhaustive events, X_i (i=1,3...,m) and Y_j(j=1,3...,n) with marginal probability $p(Yj|I)$ and conditional probability, $p(X_i | Y_j, I)$. Bayes' rule is

may be used to calculate remaining marginal and conditional probabilities. This is a similar process to reversing the order of nodes in a decision tree (McNamee & Celona:1990). The joint probability, in terms of the given probabilities may be written as:

$$p(X_iY_j|I) = p(X_i \mid Y_j,I)\, p(Y_j|I)$$

Needless to say, this joint probability may be written in reverse order, such that:

$$p(X_iY_j|I) = p(Y_j \mid X_i,I)\, p(X_i|I)$$

Conditional probability is solved by equating the right hand side of the equations, such that:

$$p(Y_j \mid X_i,I) = \frac{p(X_iY_j|I)\, p(Y_j|I)}{p(X_i|I)}$$

However, $p(X_i|I)$ is unknown; this is obtained by making use of the Expansion Theorem

$$p(X_i|I) = \sum_{j=1}^{n} p(Xi,Yj|I)$$

The joint probabilities on the right hand side of the equation can now be written in terms of the known conditional and marginal probabilities. Probabilities are then written in terms of known quantities:

$$p(X_i|I) = \sum_{j=1}^{n} p(X_i,|Y_jI)\, p(Y_j|I)$$

$$p(Y_j \mid X_i,I) = \frac{p(X_i|Yj,I)\, p(Y_j|I)}{\sum_{jk=1}^{n} p(X_i|Y_k,I)\, p(Y_k|I)}$$

Bayes' Theorem may be used to revise decision-maker's estimates of probability values

3-3.2 Probability estimates in healthcare

The probability estimates for the occurrence of events in healthcare is obtained from a variety of sources, which include published studies and expert opinion.

3-3.2 (a) Published studies

Sources may be used if the published studies represent an authoritative opinion and is accepted by the wider academic community to be the authority on the particular subject. Nevertheless, other studies should be used to provide a range of probability estimates. Alternatively, if there is a single published study this may be used as the baseline probability. Further, the range for the probability may be based on a 95% confidence interval. However, if this is the case, it should be made clear at the outset of the analysis that a single source for the probability value has been used. A particular study may be chosen due to its size, and other studies in the same topic may add little to the knowledge base.

Another reason for choosing a particular study or type of study may depend on whether or not the results of the decision analysis are to be generalised to a wider population. If this is the case, then it is important that any studies used for probability estimates do actually represent the population to which the results will be generalised.

Information may be collected from multiple numbers of studies in order to obtain the best approximation. Simple calculations can be made to obtain mean probability values. However, the disadvantage of such an informal method is that the size of studies will not be considered and thus the results may be biased. Alternatively, a meta-analysis may already exist, otherwise it may be feasible to carry out such an analysis as part of the overall cost-effectiveness analysis. It is a systematic method, which reduces bias of study results. Additionally, meta-analysis takes account of the size of the studies and finally meta-analysis improves the possibility of reproducing the analysis.

3-3.2 (b) Expert panels

When published data is not available, experts on the subject may be approached for their personal views on probability. Expert opinion may be sought in the form of Delphi panels, modified Delphi panels, and nominal group processes and expert panels. The latter of these usually incorporate experts' opinion either through face-to-face interviews, or questionnaires. Expert opinion is most widely used in decision analyses and Markov models.

Delphi panels are separated into different types, classic, real-time, policy and decision panels. These panels operate in stages or rounds, in an effort to obtain a convergence of opinion in a particular area (Evans, 1996). A group of experts are identified and sent a questionnaire. Further, if there is a large discrepancy in the choice of probability values, experts are given the opportunity to revise their views in the light of additional information. Anonymity of respondents is maintained in all stages, and is a key feature of Delphi panels.

However, a problem with obtaining expert opinion in more than one round is the potential for experts to drop out of the study. Thus, in a Delphi panel, experts may decide to opt out after the first round of questions and therefore the results may be biased. There is some evidence to suggest that studies with higher numbers of experts has a relatively high rate of drop outs, yet studies with a small group of experts have a much lower drop-out rate (Evans, 1996).

3-3.3 Levels of uncertainty in probability estimates

Decision analysis relies on the validity of estimates used for probability values. Often, many different probabilities are used, thus even small errors in these values can cause a large and erroneous effect on the final outcome of the analysis.

The level of uncertainty in the probability estimates on the conclusions of the decision analysis is measured by sensitivity analysis (Pettiti,1993: 154). However, sensitivity analysis is difficult to perform when three or more probabilities are varied at the same time. A number of statistical and quasi-statistical methods are available to estimate this level of uncertainty. These methods attempt to measure a type of confidence range, which is an approximation of the equivalent confidence interval used in classical statistical techniques.

3-3.4 Rifkin 1983; Doubilet et. al. 1985; Critchfield & Willard 1986

Methods used by Rifkin, Doubilet and Critchfield assume a probability density function associated with the variables of probability and outcome measures. Each density function has a mean and standard deviation. The mean of the probability density function equals the probability estimate. Where the standard deviation represents the level of uncertainty in the probability estimate. It is relatively simple to calculate the probability density function for the expected outcome. However, complex decision trees are much more difficult. In practice, the probability density function is obtained using Monte Carlo Simulation. It is crucial to obtain a density function for each of the variables and is often time consuming to perform. Additionally, empirical data on probability density functions may not be available for many of the variables. Thus, the choice of a density function relies on guesswork or the adoption of a convenient

probability density function. For example, Doubilet et. al. suggest the adoption of a density function which follows a logistic-normal distribution for decision analysis.

3-3.5 Confidence Profile Method (CPM)

Confidence profile method (CPM) is based on Bayesian statistics is described by Eddy (1989). It is particularly useful for estimating level of uncertainty in a meta-analysis. However, it is more appropriate in a decision analysis when multiple sources are used to estimate the clinical outcome of a problem. Similar to previous methods, the CPM yields a number comparable with the 95% confidence interval used in classical statistics. Additionally, the CPM is capable of taking into account the bias in individual studies along with differences in the level of uncertainty for estimates of the study parameters.

The statistical (and quasi-statistical) methods have not applied widely in the estimation of levels of uncertainty for probability estimates. The calculation of a probability density function is a complex and demanding task, even where the advice of an expert panel is sought. In comparison, the Bayesian methods are more attractive for use in both meta-analysis and decision analysis. However, there is little empirical work in this area. Sensitivity analysis is the most widely used method even though a precise estimate of the level of uncertainty is not obtained. Nevertheless, because methods, which do claim to estimate such figures, are poorly developed and lack empirical work, sensitivity analysis appears to be the best option.

3-3.6 Markov models

Markov models are used in decision analysis in order to describe complex decision problems involving transitions into various states of health. There are two types of

Markov models; Markov chains and Markov processes. The first type of model, Markov chains assume that the probabilities of transition are constant over time. The second type of model, Markov process, assumes that the probabilities of transition vary over time. Assuming constant transition probabilities is useful for acute or short-term illness. However, if the disease is long-term, probabilities dependent on time are more applicable. Markov chains are a subset of the more general Markov process. A Markov model is one of several mathematical models that may be used in decision analysis. Its advantage lies in the simplicity of the model and the ability to accurately mirror many clinical problems. The Markov model can replace a decision tree outright or can be grafted onto standard decision analysis as an equivalent to the utility structure (Beck & Pauker, 1983:420)

There are essentially four stages when using Markov models in a decision analysis model to display complex decision problems (Pettiti, 1993:143). Stage one requires the identification of the various stages of health to be modelled. Further, ways in which patients enter or leave a particular state of health are defined. Stage two involves defining the length of a cycle for transitions into and out of various states of health. The third stage requires an estimation of transition probabilities. Essentially, these methods are the same as those used to estimate other probabilities in decision analysis. Finally, the outcome with and without treatment is estimated using one of three methods.

3-3.6 (a) Markovian assumption

This is fundamental to an analysis with a Markov model. Essentially, this assumption states that each transition state takes place independently of any preceding transitions. Thus, in a graphical presentation, each oval/circle depicts a single transition from one

state to another. If a patient is moderately ill, this information is sufficient to predict future transitions to death or severe illness. Thus,

'...all patients in a given state at a given time have the same prognosis, no matter how they got to the present state.' (Beck & Pauker, 1993:421)

However, there are few biological situations where this applies. Nevertheless, the Markov model has been shown to provide an accurate prognosis of disease.

3-3.6 (b) States & transitions

A Markov process is conventionally represented graphically. The different states of health are defined as ovals/circles and time is shown vertically, on the left side of the graph. Transition states should be defined by probabilities or by their medical prognosis, correspond to standard or literature based definitions of state of disease and finally organised into 'allowable' states of disease. The 'allowable' transitions of health states are shown with arrows to link the different states.

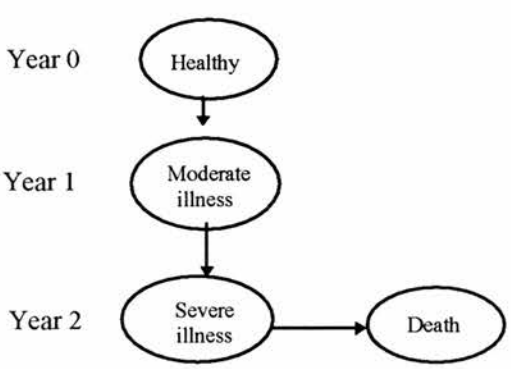

Figure 3.7: Hypothetical Markov process

Figure 3.7 shows hypothetical transition states healthy, moderate illness, severe illness and death. As figure shows, it is possible to reach state of death from any other states. Death is defined as an *absorbing* state, as it is not possible to move to any other state and all other states are *non-absorbing*. If all the patients in the cycle reach state of death, the Markov cycle is said to be absorbed.

3-3.6 (c) Cycle length

This is the period of time between evaluations of outcomes and will depend on the type of disease being modelled. For acute illness, the period chosen may be days or weeks, for chronic disease the time period for evaluations may be yearly. A number of computer programmes are available to facilitate calculation of cycles. In the previous, hypothetical example, time periods chosen were years i.e. the outcome of treatment is evaluated at the end of each year.

3-3.6 (d) Transition probabilities

A common source for identifying probabilities is literature. Clinical information on patients moving from one health state to another is not usually expressed in probabilities, instead transition rates are used. The main difference between rates and probabilities is that values for probability range between 0 and 1. Values for rates can range between 0 and infinity per unit of time. The latter type of data is translated into probability values using the following formula:

$$P = 1 - e^{-rt}$$

where e is the base of the natural logarithm. The rate, r is used to estimate a transition probability p of an event over time period t.

For example, if the rate at which patients in state A move to state B is 38 per 100 per year, the transition probability of moving from state A to state B is calculated as follows:

$$P_{a/b} = 1 - e^{-38} = 1-$$

Thus, the transition probability of moving from state A to state B is

3-3.6 (e) Estimate outcomes

Beck, & Pauker (1983) outline a number of different methods which may be used to calculate life expectancy for a Markov process model. Three of the main methods are:

Monte Carlo simulation, Markov cohort (analysis of a hypothetical cohort of patients) and matrix algebra.

3-3.7 Monte Carlo simulation

Monte Carlo methods represent a branch of mathematics, which looks at experiments on random numbers. These methods have been used in fields such as operational research, medicine and nuclear physics. There are two types of problems, which may be handled by the Monte Carlo methods; probabilistic or deterministic. The method in the case of a problem that may be classified as probablist requires observation of random numbers (which represent the original problem) and then to infer a solution. In the case of a deterministic problem, Monte Carlo (sophisticated) method involves solving the original problem by simulation of a secondary problem.

Monte Carlo work is concerned with estimating the unknown numerical value (estimand) of some parameter of a distribution. The estimand is a parameter of the distribution of the random variables constituting the sample size. Monte Carlo work aims to obtain a respectably small standard error in the final result by a careful design of the way in which the data is collected and analysed. The simplest form of Monte Carlo methods is the direct simulation of a probabilistic problem and remains one of the most widely used methods.

An early example of direct simulation using the Monte Carlo method was applied to the control of floodwater and for the construction of dams on the Nile in 1957, see 'Calculating machine. Electronics applied to water storage on the Nile' *The Times* (22 March 1957), London. The issue is probabilistic because the quantity of water in the river will vary, from season to season. Data used in the analysis included records of weather, rainfall, and water levels for 48 years. The main problem is what

will happen to the levels of water in the Nile if dams or other policies are implemented. Other methods of Monte Carlo simulation include fixed, sequential and stratified sampling. However, these methods are not discussed here

3-3.7 (a) Markov cohort

Similar to the Monte Carlo simulation, the Markov cohort is also a simulation of patients. However, unlike Monte Carlo simulation, it does not follow patients individually. Instead a cohort of patients is followed, as a cohort with an initial distribution of states. At each subsequent cycle of the process, the patients are re-allocated states based on transition probabilities. The expected amount of time spent in each state is calculated by dividing the total number of patient cycles for each transition, by the number of total patients in original cohort. Life expectancy is then simply the sum of these expected values. If appropriate, these values are adjusted for differences in utilities associated with different states. Although, the Markov cohort method allows for the inclusion of time-dependent probabilities and utilities, it cannot like the Monte Carlo simulation, provide information on the distribution or variance of expected values.

3-3.7 (b) Matrix algebra

In this method, a matrix is constructed to show transition probabilities from one state to another. Table 3.1 illustrates a hypothetical example of a Markov matrix.

	Healthy	Ill	Death
Healthy	0.4	0.2	0.1
Ill	0	0.4	0.2
Death	0	0	1

Table 3.1: A Markov matrix

The probability of staying alive, for a patient who is in the severe illness category is

0 +0.1+0.5 = 0.6. The non-absorbing states in the matrix table are manipulated using an identity matrix; this is a 2 by 2 matrix with 1's shown diagonally and 0's elsewhere. Using a technique of linear algebra (matrix inversion), a new matrix is constructed.

$$N = (1-Q)^{-1}$$

The N matrix is the fundamental matrix of an absorbing chain showing the expected time in each state before absorption (death). Essentially, this method is equivalent to taking the reciprocal of a transition probability.[2]

1	0
0	1

Table 3.2 Identity matrix

However, this method is only suitable for Markov chains as it is based on the use of constant transition probabilities. The fundamental matrix is more complex than other methods, however, it has some important advantages. Firstly, it is quick to calculate, as time is not spent on simulation. This is made simpler with the aid of programmable calculators, which can invert matrices of up to five rows. Additionally, the problems of how many patients to simulate in a Monte Carlo simulation and when to terminate a Markov cohort model are not encountered.

[2] This is similar to the DEALE method already described.

Section 3-4

Modelling Utility in health

3-4.1 Concept of utility in health

The standard outcomes discussed in formal decision analysis are generally related to life or death measures. Alternatively, outcomes, which are closely related to life or death, such as years of life, saved, life expectancy or years of life lost. However, many medical interventions may reduce the likelihood of disability without affecting mortality. Treatments may also increase life expectancy, yet at the cost of disability or impaired functioning. Utility analysis is a decision analysis incorporating the values of outcomes other than death.

Utility is defined as a preference for a given outcome. This in turn is based upon the level of satisfaction, or otherwise, related to the outcome. Utility analysis allows the incorporation of individuals' preferences for different health states. However, some utility analyses are used to estimate the effects of treatment on the overall quality adjusted life expectancy. Thus, allowing the analysis to consider effects on aspects other than health.

3-4.2 Measuring preferences for health states

Different states of health are measured using various types of measurement scales. In general, scales are rated between 0 for the lowest value and one, for the highest value, in order to incorporates these values into a decision analysis. The scale may be used to adjust the life expectancy, thus obtaining a quality adjusted life expectancy as the outcome of the decision analysis. Alternatively, the values of the scale may be used to represent the outcomes of the interventions, or simply as the outcomes themselves.

The main requirements of a scale to measure preferences for health states should be reliable and valid (Pettiti, 1993:159). A scale meets the criteria of 'validity' if it has been demonstrated to measures the levels of satisfaction it sets out to measure. Types of validity are criterion validity and construct validity (Spitzer, 1987). The scale is reliable if the results of the scale are the same each time a particular health state is measured. It requires a comparison of the measure with other known measures for the specific concept or levels of satisfaction which are being measured. Thus, a pre-requisite for criterion validity is the existence of a 'gold-standard'. The second of these requirements, construct validity entails measuring the concept and testing its ability to predict events (Torrance, 1976). However, construct validity is rarely evaluated in the literature. Instead, a method of convergence (similarity of scores using different methods) is used to demonstrate existence of construct validity.

Table 3.3: Measurement Scales

Types of scales	**Description**	**Example**
Nominal	States are assigned to categories without numerical meaning	Religion: Christian, Jewish, Muslim
Ordinal	States are rank-ordered, but the distance between ranks does not have a numerical interpretation	Health status: excellent, good, fair, poor.
Interval	States are rank-ordered, and the distance between ranks provides some information on the amount of difference between ranks	Beck depression scale
Ratio	States are rank-ordered, and the distance between different points on the scale provides information on the amount of difference between ranks	Temperature

Source: Pettiti, 1993:160 (adapted)

The different types of scales are classified as nominal, ordinal, interval and ratio. Table 3.3 shows the different types of scales. Methods for the development of scales may be

separated into two main categories, holistic strategies and multi-attribute strategies.

3-4.2 (a) Holistic methods (Froberg & Kane, 1989)

These methods require the person rating the scales to all possible health states, which are to be measured. However, if there are a large number of health states to be rated, this will place a heavy burden on the respondents.

3-4.2 (b) Multi-attribute methods (Pliskin, Shepard, Weinstein 1980)

These methods make use of statistical techniques to develop a rating scale on either single attributes of health states or a combination of health states. Here, values for health states are obtained without the need to measure each state. However, the statistical techniques necessary to elicit rating scales from measurements of health states are complex. See Torrance 1982, Boyle & Torrance 1984 for more details.

3-4.3 Developing scales to measure preferences for health states

There are three basic steps in the construction of a scale to measure preferences for different states of health. The first step requires the identification of states of health to be measured. Secondly, preferences for the different states of health are elicited from an individual or group of persons. In the final stage, the data is used to construct the scale.

In general, those health states appropriate for the analysis will be defined. Thus, all health states appropriated to a particular treatment or intervention will be identified. The health states are then described in terms of functional or behavioural effects. Further, information should be provided on the levels of physical health, emotional health, and functioning of everyday activities (Ware 1987). Respondents should be identified according to the type and purpose of the study (Torrance 1982). There are a

variety of methods for creating a numerical scale, the standard gamble, time trade-off, direct scaling methods, and a miscellaneous category.

3-4.3 (a) Standard gamble

The standard gamble is a derivative of decision theory. It incorporates the central elements of decision analysis, making decisions under conditions of uncertainty. The respondents are asked to choose between two alternatives. Essentially, the two alternatives represent a certain outcome (the health state to be rated) and a gamble. The latter of these options will incorporate the best possible health (with probability p) and the worst possible health state (with probability 1-p). In order to obtain a value for the health state, the probabilities are varied until the respondent is indifferent between the two options of a certain health outcome or the best possible health outcome. This procedure is repeated for each of the health states to be rated. The scale is then constructed using each of the points of indifference for the health states.

Thinking in terms of probabilities may not be an intuitive for the respondents. Often, visual aids can be used to demonstrate the probabilities associated with the gambles. Torrance (1987) describes the use of a probability wheel or a chance board in the development of rating scales. Standard gamble techniques are very time and resource consuming, thus providing limited practical value in the development of scales.

Measurement on an interval or ratio scale has not been proved, rather they are assumed. Although, there is a correlation with measures of preference based on the time trade-off method, the former of these provides higher rates consistently. Further, changes in the description of the gamble can affect the value associated with the preferences (Llewellyn-Thomas et. al. 1984).

Table 3.4: Reliability of Measurement scales

Measure of reliability	Standard gamble	Time trade-off	Rating scale	Willingness to pay
Intra-rater	0.77	0.77 - 0.88	0.70 - 0.94	
Test re-test				
1 wk	0.80	0.87	0.77	
1 year	0.53	0.62	0.49	0.25
Inter-rater			0.75 - 0.77	

Source: Froberg and Kane (1989)

3-4.3 (b) Contingent valuation

The value of health care is increasingly measured according to an individual's 'willingness to pay' (WTP) or 'willingness to accept' (WTA) This requires the rater to specify an exact quantity of money they would be willing to pay, in order to have full health for the former method. In the latter method, the rater is required to quantify the minimum amount of money they would be willing to accept in order to tolerate a reduction in health care. These methods have been used in three ways; value prevention of health, value treatments ore services and in the valuation of health outcomes or states (Morrison & Gyldmark, 1992). However Morrison and Gyldmark (1992) point out a number of methodological shortcomings. One of the main concerns is that of selection bias when respondents are identified. In particular, the preferences of wealthier raters will hold more weight than less wealthy individuals. In addition, although contingent valuation (CV) has been used for evaluating very different types of health 'goods', it should not be assumed that they can be easily compared.

3-4.3 (c) Time trade-off

Torrance, Thomas and Sackett (1972) developed the time trade-off method. Like the standard gamble, this method also provides the respondent with a choice between two options. In this case however, the choice is between two certain outcomes rather than one certain outcome and one uncertain (risky) outcome.

Visual aids can also be used, see Torrance (1987). The main advantage of the time trade-off method is the intuitive approach of giving up life years for a certain health outcome, rather than taking a risky gamble. However, in terms of workload, the time trade-off method is just as time consuming, as the procedure must be repeated for each health state to be evaluated. Table 3.3 shows, in terms of reliability, such scales are rarely subjected to a critique. Torrance (1987) shows a good inter-rater reliability in comparison to the standard gamble. In addition, re-test reliability is good in the short term; however, in the long term re-test reliability is poor (Frober & Kane, 1989)

Measurement on the ratio or interval scales for the time trade-off method is not known. Although, both sets of scales, the time trade-off and standard gamble are reasonably correlated, this does not necessarily prove that they really do measure what they claim to measure. Correlation simply proves that both scales are essentially the same, and does not prove validity.

3-4.3 (d) Direct rating scales (DRS)

These are most commonly used to create scales. Easy to develop and simple for the respondents to understand. The most commonly used DRS's are Interval scaling, category rating and magnitude estimation scales (Frober & Kane 1989). Respondents are asked to separate different health states into a number of specified categories. Changes between categories are assumed to be of equal preference. For magnitude estimation, respondents are asked to classify all health states against a 'standard' health state with a number or ratio to indicate how much better or worse each health state is relative to the standard. An example of a widely used direct rating scale in health assessments is the EQ-5D, initially called the EuroQol. The EQ-5D consists of 5 health dimensions, each dimension containing three levels, reflecting 'no problem', 'some problem' and 'extreme problem' and allows respondents to be classified into 1 of 243

health states (Coons et. al. 2000). In addition, the EQ-5D asks respondents to rate their health status on a scale of 0 to 100, with 0 representing the worst imaginable health state and 100 representing the best imaginable health status on a visual analogue scale (VAS). Table 3.3 shows that these methods have good intra-rater reliability and inter-rater reliability. However, these methods are much poorer than the standard gamble and the time trade-off in the test re-test reliability. Measurement of levels using these scales is assumed to be interval or ratio, however, this assumption has not been proved. Further, construct validity has not been tested. Similarly, these scale correlate reasonably well with others, but of course, this does not imply validity in itself.

3-4.4 Calculating Life expectancy

A commonly used outcome of interest in the evaluation of healthcare interventions is the expected life of the patient. This is an appropriate measure of outcome since the objective of healthcare intervention is to prolong life through the eradication or alleviation of symptoms/disease. Life expectancy may be defined as the average length of time a person is likely to survive. Statistical lifetables based on specific mortality rates for age, actuaries to estimate life expectancy often use sex and race. The data used to calculate life expectancy are based on census and death certificate data. Tables showing the expected life expectancy of healthy individuals are published (DOH). These data can then be incorporated into a decision analysis in order to calculate the effects on average life expectancy with or without treatment. More relevant data may be available from a RCT or a follow-up study where patients with a specific disease have had their life expectancy recorded, both where treatment has been offered and where it was not. In such cases, the data need not be altered and is transferred directly into the decision analysis. However, such data is not common and therefore published

life expectancy tables are used as a general rule. In the majority of cases, data from trials are usually in the form of mortality rates, mean or median mortality rates and five or ten-year survival rates. Often, this information is provided in the form of relative risk of mortality. Another common measure is the odds of mortality. However, the disadvantage of such data is the complexity of translating the available information into comparable data on life expectancy.

3-4.4(a) DEALE

A widely used method of estimating life expectancy based on mortality or survival data is the declining exponential approximation of life expectancy (DEALE). This method, developed by Beck et.al. (1982) uses information on estimates of the effect of disease and standard tables of vital statistics showing age, sex and race-specific life expectancy. The main advantage of this method is its simplicity in use. Further, it has been shown to be similar to estimates of life expectancy based on actuarial methods (Beck, Kassirer & Pauker, 1982).

The basic formula for calculating life expectancy requires an assumption whereby mortality has a declining exponential curve. Thus, the life expectancy of an individual of a given age, sex and race is estimated as the reciprocal of the mortality rate:

$$\text{life expectancy} = \frac{1}{\text{mortality}}$$

Using published life tables, this relationship can be used to estimate mortality for an individual with given age, sex and race:

$$m_{asr} = 1 / l_{asr}$$

where m_{asr} is the average mortality rate of an individual with given age, sex and race and l_{asr} is the life expectancy of individual with given age, sex and race according to published tables of vital statistics.

For example (Pettiti, 1993:140-141). If an intervention decreases the probability of death by 0.001 per year. The problem is to determine the effect of the intervention on life expectancy in a 45-year-old woman.

1. Determine the average life expectancy at age 45 from a table of vital statistics:

$$l_{asr} = 37.8 \text{ years}$$

2. Estimate the average mortality rate where

$$m_{asr} = 1/l_{asr}$$
$$= 1/37.8 = 0.026 \text{ per year}$$

3. Estimate the mortality rate in those who have the intervention by subtracting the mortality rate caused by the intervention from the average mortality rate.

$$m_i = m_{asr} - m$$
$$m_i = 0.026 - 0.01 = 0.025 \text{ per year}$$

4. Estimate life expectancy in those who have the intervention where

$$l_i = 1/m_i$$
$$= 1/0.025 = 40.0 \text{ yrs}$$

5. Estimate the gain in life expectancy in those with the intervention compared with those without the intervention by subtraction:

$$\text{gain in life expectancy} = 40.0 - 37.8 = 2.2 \text{ yrs}$$

When the goal of the analysis is to estimate the effect of a disease on life expectancy, the same method can be used. In this case, excess mortality from the disease m_e is added to the mortality rates specific for age, sex, and race. i.e. step 3.

$$m_d = m_{asr} + m \quad \text{and } l_d = 1/m_d$$

e.g. The effect of coronary heart disease on life expectancy in 45 year-old-women needs to be estimated. The excess mortality from coronary heart disease is

$$m_d = m_{asr} + m = 0.026 + 0.015 = 0.041$$
$$l_d = i/m_d = 1/0.041 = 24.4$$
$$37.8 - 24.4 = 13.4 \text{ yrs}^3$$

Thus, coronary heart disease reduces estimated life expectancy by 13.4 years.

3-4.5 Use of rating scales in decision analysis

Despite the problems and difficulties of constructing measurement scales and the theoretical disadvantages, these scales are increasingly being used in decision analysis and cost effectiveness analysis. A commonly used format in decision analysis is to incorporate the scale in order to adjust the outcome such that the outcome becomes quality adjusted life years, rather than the life years. Scales, which purport to measure health states, are based on the premise that these states of health are easy to identify, clearly segregated and are quantifiable. However, the currently available scales do not meet all these criteria. Further, the results of these scales have been shown to be affected by the processes, thus different scales will produce different results. In addition, even the same scales will not necessarily produce the same results when the same problem is presented a second time. At present, there is little agreement on the best method. Whose preferences should be used ? Again there is little agreement on the sample of population to be used to represent the preferences for society. Finally, is it possible for health states to have a single value for the whole population ? (Llewellyn-Thoma et. al. 1984)

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[3] : compound measures are more commonly used. However, before they can be used, they must be transferred to baseline (mortality +/- mortality due to intervention) estimates in order to use DEALE.

Section 3-5

Summary of chapter Three

This chapter has outlined the theoretical background for the methodology of decision analysis within a framework of healthcare. Methods for structuring the decision problem were outlined. Together with techniques for structuring the problem with the use of tools such as influence diagrams and decisions trees. Influence diagrams are useful in the structuring of complex problems allowing many aspects of the problem to be displayed in a compact form. However, decision trees allow for a more detailed presentation of the specific decision problem. This is a very important phase of the overall structuring of the problem; it is here that the decision-maker is able to understand the problem and all the relevant aspects of the problem. Once the problem has been defined and structured, the model must be populated with appropriate probability estimates. A common sense approach to using appropriate probability values is to ensure a systematic and structured search for the values. Further, where published sources and expert panel assessments of probability values are used it is important to use a range of values within the model. The final section of this chapter provided an overview of methods for evaluating an individual's preference for a given health outcome. Utility analysis incorporates the use of outcomes such as years of life saved or lost, life expectancy, levels of adverse side effects and disability as a direct result of treatment. A number of measurement scales for assessing levels of utility exist. Life expectancy is an important measure of the outcome of interest in health care. Commonly used methods for calculating life expectancy tables include the DEALE and Markov models.

Chapter Four

A review of the Clinical and economic literature on the management of *Chlamydia* trachomatis

The previous chapters have sought to provider the reader with a background and theoretical framework to the heart of this thesis: the management of *Chlamydia* trachomatis. The theory of decision analysis, as outlined in chapters three and four will be applied to the management of *Chlamydia*. This chapter will focus on providing the reader with an understanding of salient features, both from a clinical and an economic perspective.

The first half of this chapter, section 4-1 will be devoted to the clinical features of *Chlamydia* and its sequelae. An overview of the prevalence of *Chlamydia* presented in section 4-1.1. A review of the methods for laboratory diagnosis and detection of *C. trachomatis* infections in section 4-1.2 follows this. Subsequently, the current therapeutic options available are described in section 4-1.3. The importance and role of guidelines in the management of *Chlamydia trachomatis* infections is outlined in section 4-1.4.

The second half of this chapter provides a review of the economic literature on *Chlamydia*. This literature is categorised into a number of broad areas on aspects of the management of *Chlamydia*. Section 4-2.1 provides a focus on the economic burden of *Chlamydia*. Section two reviews the cost effectiveness of screening strategies. Section 4-2.3 outlines the cost effectiveness of screening in pregnant women. Section 4-2.4 reviews the cost effectiveness of screening in males. Section 4-2.5 outlines the cost effectiveness of partner notification. Section 4-2.6 reviews the cost effectiveness of laboratory confirmed treatment.

Section 4-1

The Clinical features of *Chlamydia* trachomatis

Chlamydia infections are common amongst young, sexually active individuals. Moreover, without proper immediate treatment, *Chlamydia* may represent a significant economic burden. Many infected individuals remain asymptomatic and transmission to other or new partners occurs frequently. When left untreated, *Chlamydia* infections may lead to potentially serious complications, which are both distressing to the patient and costly to treat. Antibiotic therapy is effective and relatively inexpensive for those patients accurately diagnosed. However, *Chlamydia* infections are often poorly managed from the initial diagnosis through to prescribing of appropriate antibiotic therapy.

4-1.1 Prevalence and Incidence of *Chlamydia* trachomatis

Chlamydia trachomatis infection is the most common bacterial sexually transmitted disease in England and Wales (Communicable Disease Report Weekly, 1996). The main features of this infection are threefold; infection is often asymptomatic, sequelae may be severe and if left untreated, infection can persist for more than a year (Brunham, 1990). Data from various surveys of individuals attending health services suggest infection may be asymptomatic in upto 70% of infected women (Zimmerman, 1990; Lycke, 1980) and in 4-11% of men (Karam, 1995; World Bank, 1993). The most serious sequelae of infection occur in women where infection with *Chlamydia* trachomatis may lead to pelvic inflammatory disease (PID), ectopic pregnancy and infertility. Further, these sequelae may have important lifetime consequences and are extremely costly to treat. According to the World Bank, *Chlamydia*infections

represent the most economically important sexually transmitted disease (STD) after HIV (World Bank, 1993).

In the European region, approximately 10 million new cases of *Chlamydia*infection occur each year (Maardh et. al. unpublished document). Further, an estimated 600 000 cases per annum of salpingitis may be caused by *Chlamydia* trachomatis and approximately 120 000 cases will remain infertile. Prevalence rates collated for the European Region range between 1% and 33% in women who are screened and 10-20% for men who undergo screening (see table 7.1). Prevalence rates in persons with signs or symptoms of infection are much higher and may be as high as 80% in men with epididymitis and 70% in women with PID.

Table 4.1: Prevalence of genital Chlamydia infections in different population groups (data compiled from some European countries), 1980-87

		***Chlamydia*-infected**
Screening		**%**
Women	Attending youth health centres	10-20
	Attending maternity clinics	1-13
	First-time pregnant	5-20
	Applicants for abortions	3-18
	Attending family planning clinics	3-12
	Prostitutes	10-33
	Healthy controls	1-4
Men	Military recruits	10-20
Patients with signs of infection		
Men		
	Urethritis	20-60
	Epididymitis	40-80
Women		
	Cervicitis	20-40
	Salpingitis	20-70
	Urinary tract infections	5-10
Infants		
	conjunctivitis	15-30

Source: Maardh et. al. (unpublished)

Studies in the UK show prevalence rates of *C. trachomatis* infection in persons aged 16 or above range between 1 % and 29% of the population (Hopwood, 1995,

Fish, 1989- see table below for a complete set of references). However, the majority of these epidemiological studies is based in specialist clinics such as genitourinary medicine (GUM), gynaecology, antenatal or family planning clinic and may therefore not represent accurate rates of prevalence and incidence in the general population.

Table 4.2: Prevalence and incidence of C. trachomatis infections in the U.K

Population	Location	Sex	Prevalence (%) (sample size)	Test	Author
General practice	London	Female	1.5 (19/765) 1.6 (12/765)	Ligase chain reaction EIA	Grun, 1997
	Sheffield	Male	6 (18/293)	EIA , DFA	Kudesia, 1993
	Glasgow	Female	3.6 (45/1267)	EIA vs. culture	Smith, 1991
	London	Female	10.7 (18/169)	DFA, culture	Longhurst, 1987
GP & antenatal clinic	London	Female	8 (19/248)	Culture	Southgate, 1983
Family planning	Manchester	Female	6 (6/101)	Culture	McCaulay, 1990
	Wirral	Female	9.1 (23/252)	EIA, DFA, culture	Hopwood, 1990
Community clinic (cervical smear)	Liverpool	Female	4.9 (57/1170) * 7.1 (7/99)+	EIA, DFA	Hopwood, 1995
GUM	London	Male	8.6 (31/356)	Culture	Zelin, 1995
	Bristol	Female	19 (154/796)	EIA vs. culture	Paul, 1995
	London	Female	29 (38-182)	DFA	Hay, 1994
	Birmingham	Male	16.1 (68/422)	EIA vs. culture	Matthews, 1989
	Bristol	Female	19 (154/796)	Culture	Richmond, 1980
	London	Female	20.4 (58/284)	Culture	Oriel, 1978
GUM & antenatal	Liverpool	Male	7 (18/252)	Culture	Wood, 1984
Gynaecology	Kent	Female	6.3 (102/1611)	EIA	Edet, 1993
	London	Female	3.6 (45/1267)	Culture	Fish, 1989
Abortion clinic	Swansea	Female	9 (32/400)	EIA	Blackwell, 1993
	Liverpool	Female	11 (19/167)	Culture	Duthie, 1987
	London	Female	7.8 (7/89)	Culture	Ridgway, 1983
Colposcopy	Glasgow	Female	6 (6/101)	Culture	Smith, 1991

* referred to GUM clinic
+ symptoms of infection
Source: adapted from Simms et. al. 1997: p 124

A recent study reviewed databases to identify incidence of *C. trachomatis* infection in England and Wales (Simms et. al. 1997). This study utilised two types of routine surveillance data; (1) Department of Health and the Welsh office records of *C.*

trachomatis infections from GUM clinics, (2) Communicable Disease Surveillance Centre (CDSC) reports of *C. trachomatis* infection submitted by microbiologists in England and Wales on a voluntary basis. The numbers of new cases of genital *C. trachomatis* infections for the period 1989 to 1994 were then combined with the estimated mid-year resident population of both countries. The results from GUM clinics showed considerable variation in the prevalence of *C. trachomatis* infection detected within different clinical settings. Overall, there was a significant linear decrease in attendance rates for both men and women throughout the 5-year period. The rates of infection for women are higher than for men. In 1989, the rate of new cases for *C. trachomatis* infection in women was between 115 and 135 per 100 000 however by 1994 the rate of new infections had decreased, representing between 90 and 130 per 100 000. Women aged 16-19 had the highest attendance rates at GUM clinics. In this age group, new cases of *Chlamydia*infection were approximately 370 per 100 000. Similarly, the rate of new *Chlamydia*infections decreased from 88 to 100 per 100 000 in 1989 to 90 per 100 000 by 1994. The highest attendance rates were recorded in men aged 20-24. In this age group, *Chlamydia*infections were approximately 225 per 100 000. Data taken from laboratory reports of *Chlamydia*infections shows an increase in the number of new cases of infections over the period 1981 to 1994. For women, the rate of new cases increases from 4 per 100,000 in 1981 to 14 per 100 000 in 1994. In men, there is an increase from 3 to 6 per 100 000. Despite this overall increase in new cases of infection, the data shows a steady increase from 1981 to 1985 and then a decrease. The highest rates of new cases in women were seen in those aged 20-24. For men, the highest rates of new cases were seen in those aged 25-34.

Although, a clear increase in the incidence and prevalence of *Chlamydia* infections has been noted, it remains unclear whether this is due to changes in the actual prevalence and incidence rates or due to improvements in the methods for detection and diagnosis of infection, collecting and reporting of data.

Similar rates of prevalence and incidence have been reported in other industrialised countries. The Center for Disease Control (CDC) in the US has reported an annual incidence of 4 million *Chlamydia*infections (MMWR, 1993). Epidemiological studies have identified age as the single most important factor in predicting infection. The highest incidence of *C. trachomatis* occurs in women below the age of 25 years(Saxer, 1989; Willard, 1989; Root, 1991 & Stergachis, 1993, Buhaug, 1990; Avonts, 1989; Bro, 1990; Brannstrom, 1992) . Many women will be asymptomatic and therefore will remain undiagnosed and untreated. Prevalence in this age group may be as high as 10% (Marra, C., 1998). Other risk factors for infection include single marital status, multiple sexual partners, lower socio-economic status and concurrent *Neisseria gonorrhoeae* infection (MMWR, 1993).

Prevalence in men has been even more difficult to determine, studies in North America, Australia and the UK suggest prevalence rates between 8-20% in asymptomatic men and adolescent boys (McNagny, 1992; Rietmeijer, 1991; Stamm, 1984; Shafer, 1987 & Brady, 1988). The main risk factors for infection in sexually active adolescent males and females are age, multiple sexual partners and concurrent N. gonorrhoeae infection. The long-term consequences and morbidity of infection is more serious in women than in men. A high proportion of women is infected with PID. In the US, approximately 10-40-% of women may become infected with PID with 1 million cases of PID diagnosed annually (MMWR, 1991:40). There is a strong relationship between PID and *C. trachomatis*. In Sweden, studies have demonstrated a

reduction in PID and N. gonorrhoeae have correlated with substantial reductions in PID morbidity and associated costs (Westrom, 1988; Kamwendo, 1996).

A comparison of the various epidemiological surveys and studies both within the U.K and across different countries is fraught with difficulties. Studies are often based on a small sample of individuals, use a variety of sampling methodologies, are often based in clinical settings atypical of the wider population and often employ a wide variety of methods for the detection of infection. Furthermore, there is a large pool of asymptomatic infections which are seen in settings other than GUM clinics or which remain undiagnosed. Population estimates suggest that only 10% of infections are identified in GUM clinics (NHS executive). The methods used for detection may be critical in determining accurate prevalence and incidence rates of infection since tests will differ in their sensitivity and specificity thereby influencing the number of positive cases identified accurately. The limitations of these epidemiological studies suggest that figures identified are not absolute levels and therefore interpretation or risk factor data is difficult as are comparisons between studies. Finally, the extrapolation of results from epidemiological studies to the wider population should be viewed with caution.

4-1.2 Clinical spectrum

Infection is often asymptomatic in upto 70% of women (Zimmerman, 1990, Lycke, 1980). Commonly encountered symptoms include post-coital bleeding, yellow discharge and an easily bleeding cervix. Other manifestations of the lower genital tract include acute urethral syndrome and proctitis. An estimated 10% of infections reach the upper genital tract (Westrom 1982 in Marra, 1998). Approximately 20-40% of women may become infected with PID, if adequate treatment is not provided. Further complications of PID include ectopic pregnancies (10%), infertility (17%), and chronic pelvic pain (17%) (Westrom, 1992; Jones, 1982 in Marra, 1998). Main symptoms of

PID include lower abdominal pain, however, symptomatic PID which accounts for detectable salpingitis represents less than 25% of the total number of cases. More than 50% of infertile women with serological evidence of *Chlamydia* infection do not experience symptoms of PID (MMWR, 1993, Westrom, 1992; Jones, 1982). Approximately 25% of all PID infections result in complications such as infertility, ectopic pregnancy and chronic pelvic pain (Trachtenberg, 1988).

Infection may be asymptomatic in upto 25% of infected men (Stamm, 1984). *Chlamydia* is a common cause of nongonococcal urethritis (NGU) accounting for between 23% and 55% of NGU infections (Stamm,1984). When present, clinical symptoms include mild dysuria, and discharge that may be white, grey or clear in colour (Weinstock 1994). Men with NGU may develop epididymitis, however the proportion remains relatively low at 1-2% (symptoms include scrotal pain/swelling, tenderness and fever). *Chlamydia* can also result in acute prostatis or proctitis (symptoms include perineal pain, dysuria, increased urinary frequency and urethral discharge). Proctitis can occur in men practising receptive anal intercourse. Symptoms for proctitis include anorectal pain and tenesmus (rectal sensation of incomplete defecation). However, the long-term complications of *Chlamydia* in men are rare and include Reiter's syndrome, tenosynmovitis, uveitis and urethritis.

4-1.3 Laboratory Diagnosis of *C. trachomatis* infection

There are two main types of tests for a laboratory diagnosis of *Chlamydia*, culture and non-culture methods. The 'gold standard' for detection is the isolation of *C. trachomatis* from cell culture although in recent years, several non-culture tests have been developed (see table 4.1). Black (1997) conducted an excellent review to compare and contrast the different types of tests for the detection of *Chlamydia*. The key findings of this review are discussed below, however the reader is referred to Black (1997) for a full review.

4-1.3 (a) Cell Culture Methods

This method has the advantage of detecting viable *Chlamydia* organisms and an excellent specificity of 100% (Jones, R 1989 in Marra). This type of method can be used in low prevalence populations. Additionally, cell culture methods have been shown to be able to detect urethral specimens from women and asymptomatic men, vaginal specimens from women and nasopharnageal specimens from infants (MMWR, 1993). The disadvantages of cell culture methods include low sensitivity, 70-85%, high level of technical expertise, cold transportation of specimens, and length of time required to obtain results (3-7 days) and the high costs of performing the test (Mahoney, 1985)

4-1.3(b) Non-culture tests

Non-culture tests have been developed in response to the difficulties with cell culture tests and other technical difficulties. Such tests are relatively easy to perform as they do not require handling of specimens and are generally cheaper than cell culture tests. The most commonly used tests for high volume laboratories include antigen-detection methods and non-nucleic acid amplification technologies :

(1) Direct fluorescent antibody (DFA) staining and enzyme immunosorbent assay (EIA) which are used to detect antigen

(2) Detection of nucleic acid e.g. ribosomal RNA detection by hybridisation with a DNA probe and detection of *Chlamydia*DNA by amplification with polymerase chain reactions (PCRs) or ligase chain reactions (LCRs)

(3) Enzyme leucocyte esterase (LE) in urine

(4) Serological tests

These tests are quick to perform and are therefore ideal for use in laboratories. Sensitivities for these tests reported in the literature are in excess of 70% and specificity of 95-99% in high prevalence populations (i.e. >5% prevalence). However, there are likely to be a significant proportion of false positive results in populations with prevalence below 5% (Black, 1997). Because of this, the CDC recommends that all persons with positive non-culture test results in low prevalence populations should be confirmed with other standard tests (MMWR, 1993).

The most recent tests are the nucleic acid amplification methods with polymerase chain reaction (PCR) or LCR. The specificity of both tests is above 99%. Since the positive predictive value of these tests is high, confirmation is not currently recommended. Additionally, DNA-amplification tests can be used with non-invasive specimens and still maintain high levels of sensitivity. Indeed, such methods are reported to increase detection rates by as much as 30% in both low and high prevalence populations (Black, 1997).

Serological tests include: microimmunofluorescence (MIF), indirect immunofluorescent antibody (IFA), complement fixation (CF) and enzyme-linked immunoassay (ELISA). These tests are not routinely used in detection of *Chlamydia* due to their disadvantages. The tests require a high level of technical experience and

are often laborious. In addition, tests cannot distinguish between active infection and an infection from a previous contact.

Chlamydia may be detected from urine samples with a leucocyte esterase (LE) tests. However, studies have shown that both the sensitivity and specificity are low, ranging between 31 - 83% and is not recommended for screening strategies(Black, 1997).

DFA, EIA and DNA hybridisation provide advantages of improved detection rates for widespread screening, however, higher costs are associated with confirmatory testing in low-risk populations and in asymptomatic men and women. PCR and LCR are more expensive than cell culture tests but they do not require confirmatory testing. Higher sensitivities than 'gold method' and do not require invasive specimens. Non-invasive methods such as urine tests may be more appropriate for high volume screening of asymptomatic individuals and low prevalence populations.

Table 4.3: Tests used for the detection of C. trachomatis

Laboratory test	Time	Specificity (%)	Sensitivity (%)	Disadvantages	Advantages
Cell culture	3-7 days	100	70-85	High level of technical expertise required Increased time to obtain results Decreased sensitivity Specimens should be processed within 48h Loss of 20% of organism due to process	Preserves organism for testing Detects only viable infectious *Chlamydia* antibody Minimal potential for contamination Specimens obtained have provided good sensitivity and specificity
Antigen detection methods					
Direct Fluorescent antibody (DFA)	30 min	98-99	89-90	Highly trained personnel required Intensive & laborious process Primarily used for endocervical smears	Rapid Refridgeration of specimens during transport not required Not dependent on viable organism
Enzyme immunsorbent assay (EIA)	3-4 hrs	97	85	Limited use in low prevalence populations without a blocking assay Low sensitivity in urine specimens	Rapid Refridgeration of specimens during transport not required Not dependent on viable organism
Rapid tests	30 min	95	70	Low specificity Less sensitive than other lab performed EIA	Rapid, performed in physician's office Not dependent on viable organism
Nucleic acid detection methods					
DNA hybridisation probe	2-3 hrs	98-99	85	Highly trained personnel required Less sensitive than DNA amplification tests Positive tests in low prevalence populations need to be confirmed	May be used in conjunction with test for detecting N gonorrhoea Refridgeration of specimens during transport not required Not dependent on viable organism
Polymerase chain reaction (PCR)	3-4 hrs	98	94	False negatives Low sensitivity in females Test vulnerable to contamination	Refridgeration of specimens during transport not required Approved for cervical, male urethral, male urine specimens
Ligase chain reaction (LCR)	30 min	99	94	See PCR	See PCR
Leucocyte esterase method (LE)					
LE test	5 min	85	60	Additional test required for *C. trachomatis* Does not have adequate sensitivity for specimens from women and older men	Non-invasive Urine specimen Adequate sensitivity for male specimens

Source: Black (1997) in Marra et. al., 1998: 196-197

4-1.4 Management of *Chlamydia* trachomatis

Effective treatment for infection with *C. trachomatis* is currently available, however, a major problem to successful treatment is the nature of infection. As noted in the earlier part of this chapter, infection is often asymptomatic and even in cases where symptoms are present, diagnosis based on aetiology remains difficult. Furthermore, because of the likelihood of sexual transmission and the possibility of upper genital tract infections and its sequelae (PID, infertility and ectopic pregnancy) in patients with minor symptoms or signs of infection, it is important to treat patients whenever *C. trachomatis* is diagnosed. Treatments available include various classes of antibiotics ranging from tetracyclines, penicillins, and macrolides to quinolones.

4-1.4(a) Tetracyclines

This class of antibiotics has been the mainstay of anti*Chlamydia*therapy since their introduction over 20 years ago. Prior to 1993, tetracylines were generally used as first-line agents for *C. trachomatis* infection. The most widely used drugs are doxycyline, erythromycin and minocycline. The most common side effects are gastrointestinal. However, these agents are not recommended for use in pregnant women. Clinical trials to evaluate tetracycline,, minocycline and doxycycline show efficacy rates between 83 and 100% (Oriel 1983; Nilson 1992). In the case of erythromycin, clinical trials have demonstrated efficacy ranging from 63-100% in men and slightly higher in women, 66-100% (Bowie, 1982; Brunham, 1982 Walsh, 1987). Additionally, a higher efficacy rate has been reported in studies comparing the 1g/day dose with 2 g/day for the higher dosage (Linneman, 1983; Robson, 1983 in Marra). However, higher doses also have a higher level of side effects associated with them such as higher gastrointestinal side effects. This in turn was shown to affect levels of compliance with therapy.

4-1.4(b) Quinolones

The first generation quinolones such as ciprofloxacin, norfloxacin, fleroxacin, lomefloxacin and pefloxacin have been somewhat disappointing (Bandolier, 1998). However, ofloxacin has excellent in vitro activity against *C. trachomatis*, with MICs ranging from 0.5 to 2mg/L and is superior to ciprofloxacin (Jones, 1991). Clinical trials have shown ofloxacin 200mg or 400 mg twice daily for 5-10 days is as efficacious as doxycycline 100mg orally twice daily for 7 days. The efficacy rates range between 97% and 100% in men with urethritis and women with cervicitis. The most common side effects include rash, pruritus and anaphylactoid reactions. All fluoroquinolones are contraindicated in pregnant women. However, there is some controversy relating to the optimal dosage. The CDC currently recommends 300 mg twice daily for 7 days however this formulation is not available in the U.K.

4-1.4(c) Macrolides

The macrolides clarithromycin, roxithromycin and josamycin are effective in *Chlamydia*infections in standard twice daily dosing for 5-10 days. Azithromycin is the most recent antimicrobial agent for *C. trachomatis* with excellent in vitro activity (MIC 0.03 to 0.25 mg/L), has high tissue concentration after oral administration and has a long tissue half-life (3 days) thus allowing for single-dose treatment (Foulds, 1990 & Jones, 1991). Clinical trials have demonstrated efficacy rates similar to doxycyline administered twice daily Nausea, diarrhoea and abdominal pain were the most common side effects for both drugs.

4-1.4(d) Penicillins

Penicillins continue to be used despite controversy in the medical literature. The CDC recommends the use of amoxycillin 500mg three times daily for 5-10 days for pregnant women. No other penicillins or cephalosporins are used in the management of *C. trachomatis*.

4-1.4(e) Compliance

There is limited research on compliance rates of antibiotic therapy for *Chlamydia*, however two recent studies of compliance with doxycyline report non-compliance rates as high as 70% in an electronically measured study much higher than self-reported non-compliance rates of 44%(Bachmann, 1996 & Augenbraum, 1996 in Marra). No published data on compliance with ofloxacin however likely to be similar to doxycyline since dosage is the same (twice daily for 7 days). Erythromycin is not tolerated well at higher doses of 2 g daily; upto 71% of patients suffer side effects and which may be a contributing factor to increased non-compliance (Linneman, 1987 in Marra). Azithromycin compliance can be safely assumed to equal 100% if the 1g single dose is administered under the supervision of a healthcare professional.

Section 4-2

Guidelines for management of infection

Infections are asymptomatic in upto 70% of women and 50% of men (Zimmerman, 1990; Lycke, 1980) and sequelae may be severe if left untreated (Brunham, 1990). In addition, infections may be managed in a variety of health services including primary care, GUM clinics and secondary care whilst encompassing a wide range of health professionals. *Chlamydia* is a common STI however it is often poorly managed in part related to the difficulties of diagnosing and detecting asymptomatic infections. A common failing is that of notifying and treating partners so that re-infection occurs (Fitzgerald et. al. 1998). Moreover, variation in clinical practice has been reported in a number of published studies (see below). The Scottish Needs Assessment Programme (SNAP) under the auspices of the Scottish Inter-collegiate Guidelines Network (SIGN) found clear evidence of variation in clinical practice (SIGN, 1997):

- Facilities for routine contact tracing of *Chlamydia*infection other than GUM clinics vary in Scotland.
- Despite similar prevalence rates for gonococcal and *Chlamydia*infections in Scotland, GPs tests for *Chlamydia* is approximately 2/3 less than tests for gonococcal infections.
- Less than half of all gynaecology units in Scotland screen for *Chlamydia* prior to termination of pregnancy.

In England and Wales, further evidence of the variation in clinical practice can be found:

- Referral of infected persons to a health advisor varies considerably between practices. In one study, the authors found referral rates for patients ranged between 59-100% in an audit of the Wessex region (Priestley, C. 1998)
- The proportion of contacts seen within 14 days varied between clinics from 16% to 50% and the proportion seen within 28 days varied between 32% and 51% (Priestley, 1998)
- Drug treatments varied between and within clinics (Priestley, 1998) although most treatments were effective, with 96% of patients who were followed-up cured – does suggest a lack of treatment protocols and variation in individual preferences for drugs (Priestley, 1998)
- Recording of information for follow-up of contacts showed a wide variation in clinical practice, ranging between 50-100% in an audit conducted in East Anglia (Sonnex & Williams, 1998)
- Contact assessment by a clinician varied between 33-103% in East Anglia (Sonnex & Williams, 1998)
- Rates of re-attendance for test of cure varied in a multi-district audit conducted in Yorkshire, from 50-82% (Monteiro et. al. 1997). Reasons for this are not clear however there is evidence from a study conducted in Edinburgh to suggest that time off work is an important factor (Ross et. al. 1995)
- Contact tracing policy varied in a survey of GUM clinics in England and Wales, ranging from 30-91% (Stokes & Schober, 1999) A district general hospital in Bolton reported rates of 70% (Rani et. al. 1999)

Whilst part of the variation may reflect differences between populations, undoubted there remains variation due to differing diagnostic and management policies. Thus the

.public health importance of managing infections appropriately through development of guidelines is clear.

4-2.1 UK guidelines

A number of guidelines have been developed in the UK including those developed by Fitzgerald et. al. (1997), Scholes et. al. (1998), Stokes et. al. (1999) and SIGN (2000). The most recent of these guidelines will be reviewed first:

4-2.1 (a) Scottish Inter-collegiate Guidelines Network (SIGN)

These guidelines were developed on the basis of a systematic review of the evidence to answer two key questions:

- circumstances in which individuals should be screened routinely
- optimum management of patients identified as *Chlamydia* positive

The guidelines are classified into five main sections, a summary of the key findings are presented below:

Testing for patients with signs/symptoms of *Chlamydia* is recommended with nucleic acid amplification test (e.g. LCR or PCR). For asymptomatic patients, testing is recommended only where:

- women are undergoing termination of pregnancy
- all patients attending GUM clinics
- patients with another STD
- sexual partners of those with *Chlamydia*infection
- mothers of infants with *Chlamydia*conjunctivitis or pneumonitis
- all women undergoing uterine instrumentation, including IUD insertion, who have risk factors for *Chlamydia*infection
- semen and egg donors
- sexual partners of those with suspected *Chlamydia*infection

In addition, opportunistic testing should be considered in the following groups of women:

- women younger than 25 year and sexually active
- women aged 25 years or older with two or more partners in the last year or a change of sexual partner in the last year

Treatment should be initiated in symptomatic patients without waiting for laboratory confirmation of infection. Uncomplicated infection should be managed with any of the following treatments:

- azithromycin 1 g stat
- doxycyline 100 mg twice daily for 7 days
- lymecycline 300 mg once a day for 10 days
- minocycline 100 mg once a day for 9 days
- ofloxacin 200 mg twice daily for 7 days

However, when taking compliance into account, the recommended course of treatment for uncomplicated *Chlamydia* is azithromycin 1 g stat.

Follow-up should be offered routinely 2-3 wks after initiating therapy when an interview should be conducted. Where patients have complied with treatment, a test of cure may not be necessary although in some cases, particularly asymptomatic infections, patients may prefer the reassurance of a test of cure. If a test is conducted, a molecular amplification assay should be performed 3 weeks after the initiation of therapy.

All patients should be referred to trained health advisers for support with partner notification and should be given the option to choose the method in which the partner is notified. For example, an index patient informs the partner, healthcare provider contacts the partner anonymously or the healthcare provider notifies the partner if the patient has not done so within a given number of days.

In women and asymptomatic, contact all partners over the last six months

In men with symptomatic infection, contact all partners over the four weeks prior to onset of symptoms

All patients with *Chlamydia* infection should receive appropriate health education. Health education should be delivered in a wide variety of non-health care

settings. Education about *Chlamydia*infection should be integrated with other sexual health education and contraceptive provision.

4-2.1 (b)Fitzgerald et. al. (1998)

The key recommendations from the Central Audit Group are listed below:

- All new patients attending GUM clinics should be offered a test for *Chlamydia*
- Diagnostic test methods should be appropriate to the prevalence of *Chlamydia* in the population
- First line treatment should be doxycyline or deteclo.
- Second line treatment should be erythromycin 500 mg twice a day for 7 days, tetracycline 500 mg 4 times a day, ofloxacin 400 mg every day for 7 days or azithromycine 1 g stat
- Patients should receive health education on *Chlamydia*, its diagnosis and treatment
- Patients should be followed-up to check compliance with treatment and contact tracing.
- Partner notification must be taken in all cases

4-2.1 (c) Stokes et. al. (1999)

The Leicestershire *Chlamydia* Guidelines Group (Stokes et. al. 1999) develop evidence-based guidelines for management of genital *Chlamydia* infection in general practice. The guidelines were developed using a three-stage approach: (1) a postal questionnaire survey was used to determine existing knowledge among Leicestershire G.Ps and to determine management of patients within primary care, (ii) a review of the published literature on evidence relating to the management of *Chlamydia* in British practice, and (iii) information gathered from the critical review and the postal questionnaire was used to develop evidence-based guidelines by a multi-disciplinary group of experts. The key recommendations of the Group are as follows:

- Testing in males and females should be conducted where a suspicion of *Chlamydia* exists e.g. presence of 1 or more risk factors
- Testing should be conducted in women prior to termination of pregnancy
- Testing should be considered in women presenting for emergency contraception
- First line antibiotic treatment is doxycyline or azithromycin
- Second-line antibiotic treatment includes amoxycillin, erythromycin or tetracycline

- Patients who test positive should be referred to a GUM clinic for a follow-up, counselling, screening for other STDs and contact tracing

4-2.2 CDC guidelines and recommendations

The CDC guidelines focus heavily on prevention strategies and not just the management of infection, as is the case with the UK guidelines. Efforts to prevent infection with *Chlamydia* focus on reducing transmission rates and promoting behavioural changes that help to reduce the risk of acquiring infection. The CDC provide extensive recommendations for preventing *Chlamydia*infections and for reducing complications of PID (MMWR 1993). The primary prevention strategies fall into two main categories:

- Diagnosis and treatment of infected individuals before infection is transmitted to either sexual partners or neonatal. Since infection is often asymptomatic, this will require screening programmes to detect infection and referral of sex partners.
- Promotion of behavioural changes that reduce the risk of acquiring or transmitting infection. Such measures may include decreasing the number of sexual partners, delaying age at first intercourse and the use of barrier contraception.

Secondary prevention strategies focus on preventing complications in persons infected with *Chlamydia*. Of these, PID and its sequelae (infertility, ectopic pregnancy and chronic pelvic pain) is the most important complication, which should be prevented.

- Screening programmes to identify and treat asymptomatic women
- Appropriate treatment for female partners of infected males
- Using *Chlamydia* diagnostic tests and treatment, as appropriate, in persons with symptoms of mucopurulent cervicitis (MPC) and the urethral syndrome

Prevention strategies should be targeted at specific populations, namely sexually active adolescents and young adults. Strategies for prevention can be further separated into those, which are community based, and those, which are provided by the healthcare system. Community based strategies should be implemented throughout the community

since prevalence of *Chlamydia* is high amongst young adults regardless of ethnicity or geographical location. These strategies should raise general awareness of *Chlamydia* and aim to educate the importance of diagnosis and appropriate treatment. Use HIV/STD risk reduction programmes to emphasise the complications of *Chlamydia* infection. By adding another STD to the list of transmissible infections, persons may be motivated to modify behavioural factors, which are known to be risk factors for infection with *Chlamydia* (i.e. number of sexual partners, age at first intercourse and use of barrier contraceptive methods. Education of adolescents at school can play an important role in decreasing rates of infection in younger people. Although, many schools include HIV on their curriculum, few cover other STDs including *Chlamydia*.

Strategies provided by the healthcare sector should include systematic screening programmes, treatment of sexual partners and counselling for all sexually active patients about the risks of STD infections. Healthcare professionals should be trained to recognise and manage conditions that may be caused by *Chlamydia*: MPC, urethral syndrome (women) and urethritis and epididymitis (men).

Screening of women is a key component of prevention strategies as many women are asymptomatic and infection can persist for many months without detection. Family clinics represent an efficient method for screening as many sexually active women will undergo pelvic examinations, which provide an opportunity to take a specimen for *Chlamydia* testing.

Incidence of infection among women previously tested is unknown, however the rates of infection for previously infected women is as high as 39% (Jones, 1990). Thus, women under the age of 20 should be tested for infection with *Chlamydia* during each pelvic examination, unless sexual activity has been restricted to a single, monogamous partner. All other groups of women should undergo screening annually.

Sexual partners represent an important segment of infected asymptomatic persons and should be treated. Additionally, this will help to prevent re-infection. Finally, healthcare system should offer a comprehensive counselling service to educate sexually active patients regarding HIV and other STDs assess patients risk factors for infection, encourage use of barrier contraceptives and offer patients at high risk, advice on behavioural changes to reduce the risk of infection.

The literature is less clear regarding the testing of patients with conditions which may be caused by *Chlamydia* . These conditions include MPC, PID and urethral syndrome in women, and urethritis and epididymitis in men., gonococcal partners and partners of individual known to be infected with *Chlamydia* (Marra, C. 1998). Currently, the CDC recommends the treatment of these groups presumptively (MMWR, 1993)

4-2.3 Impact of guidelines

Although national guidelines for the management of *Chlamydia*, with the exception of SIGN do not exist, implementation of local guidelines has had a limited impact on the management of this patient population. A recent audit of 9 GUM and department of sexual health in East Anglia assessed management of *Chlamydia*infections with defined targets (Sonnex, 1998). Data were collected for all confirmed patients with *Chlamydia*infection for the periods January to March 1995 and 1996. The results demonstrated overall 97% of patients were informed of their diagnosis and 100% received appropriate antibiotic therapy. In addition, partner notification was discussed in the initial consultation for 99% of patients and 87% patients in the follow-up consultation. Although improvements in the management of *C. trachomatis* infections have been shown in this study, it falls short of some targets identified. One of the targets with the highest shortfall, is that of follow-up with contacts. Whilst the authors

of this study do not discuss the possible reasons for the shortfall in targets, it may be hypothesised that in this particular case, it may, in part be attributable to lack of co-operation from contacts. Nevertheless, this study demonstrates the potential impact of guidelines, however more research is required to evaluate how widely guidelines have been implemented.

4-2.4 Summary of Section

Chlamydia infections represent one of the most common sexually transmitted infections amongst the young, sexually active population. Detection and diagnosis of infection is often difficult and as a consequence is poorly managed. Symptoms are often minor and infection often remains asymptomatic, thus leading to further transmissions to the partners of infected persons and to unborn babies. The clinical sequelae for *C. trachomatis* are significant resulting in costly treatment. Although various tests to detect *C. trachomatis* are available, a test with 100% specificity and 100% sensitivity remains elusive. Treatment for *Chlamydia*infections is available in the form of antimicrobial agents. The key issues with treatment are side-effects and compliance with a full course of treatment. The sequelae of untreated infections are significant therefore it is imperative patients are diagnosed accurately and subsequently managed appropriately for *C. trachomatis* infections. A number of local guidelines for England and national guidelines for Scotland have been developed in response to the public health importance of detecting and managing *Chlamydia* appropriately. The limited evidence available suggest guidelines have had a positive impact.

Section 4-3

A Review of the Literature on the Economic Implications of *Chlamydia*

Chlamydia represents a significant economic burden mainly due to its frequent and serious sequelae, which include pelvic inflammatory disease (PID), ectopic pregnancy and infertility. As the prevalence of *Chlamydia* has increased, the costs of managing infected individuals have continued to escalate. Further, such costs are exacerbated by the lack of successful prevention and control strategies. There is limited research on the economic impact of *Chlamydia* in the UK, thus this section will focus on providing a review of its impact in other industrialised countries. Section 4-2.1 will provide an overall summary of the economic impact of *Chlamydia*. Section 4-2.2 will review studies, which have evaluated the cost-effectiveness of universal screening strategies. Section 4-2.3 will review studies that have evaluated the cost-effectiveness of selective screening strategies. Section 4-2.4 will review studies that have evaluated the cost-effectiveness of antibiotic therapy for the treatment of *Chlamydia*infections. Section 6-6 will review studies, which have evaluated the cost-effectiveness of notifying partners of infected individuals. Section 4-2.5 will review studies that have evaluated the cost effectiveness of screening strategies in pregnant women.

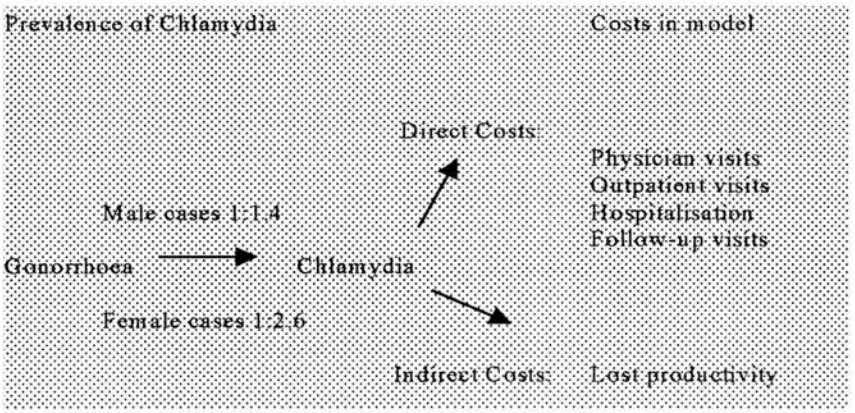
4-3.1 Economic burden of *Chlamydia*

Washington et conducted a landmark study of the economic burden of *Chlamydia* in the U.S population. al. (Washington et. al. 1987). It is interesting to note that at the time of writing this thesis, whilst numerous studies to evaluate the cost-effectiveness of treatment for *Chlamydia* have been conducted, the Washington et. al. study remains the only study of the cost of illness for *Chlamydia* in the English language.

Washington et. al. use the methodology of a prevalence-based approach to evaluate the cost of illness for *Chlamydia*. This type of methodology estimates the direct and indirect costs of *Chlamydia* accrued in a given year with the exception of

future lost earnings of those patients who die as a result of *Chlamydia* (Malek & Zabihollah, in press). This study estimates healthcare costs for *Chlamydia* in men and for *Chlamydia* and its sequelae in women. Direct estimates of the prevalence of *Chlamydia* were unavailable, therefore the authors estimate this rate using data on the incidence and prevalence of gonorrhoea obtained from local, national and state derived data. The ratio of *Chlamydia* to gonorrhoea cases is assumed to equate as 1.4:1 for men and 2.6:1 in women. The figure below represents a diagrammatic overview of the methodology.

Figure 4.1: Cost of illness model (Washington, 1987)



Direct costs were those incurred in the treatment of *C. trachomatis* infections and its sequelae whereas indirect costs were those incurred due to lost productivity as a result of infection. All direct costs were based on estimates of medical charges incurred for physician visits, outpatient visits, hospitalisations and follow-up appointments. In men, costs of *C. trachomatis* infections are attributed to cases of *Chlamydia*urethritis (based on estimates of gonorrhoea) and epididymitis were evaluated. The costs evaluated in this study were physician visits, clinic visits, emergency room visits and

hospitalisations. Indirect costs were calculated on the basis of lost productivity as a result of infection with *Chlamydia* and its sequelae. Indirect costs were assumed to be 1 lost day of productivity and 1 lost day for homemaking for each episode of *C. trachomatis* infection. For outpatient visits of epididymitis, 5 days of productivity loss, and 10 days for hospitalisations (+ equal number of days for homemaking). Lost productivity was calculated on the basis of median annual earnings, adjusted for the number of men working men. The same methodology was used for calculation of indirect costs for women. In the case of infants, indirect costs were based on lost productivity of one parent. In women, the costs of *Chlamydia* were attributed to cases of mucopurulent cervicitis, urethritis and PID (ectoptic pregnancy, infertility and death). Authors used an estimated 40% of PID cases caused by *C. trachomatis*. For mucopurulent cervicitis and urethritis, estimates were based on similar methodology to that used for urethritis in men. The authors assumed 2.6 cases of *Chlamydia* for every diagnosed case of gonorrhoea.

The analysis demonstrates an economic burden of $1.4 billion (1987 dollars) annually. When these costs are updated to 1998 values, they represent a total cost of $2.64[4]. The vast proportion of costs is attributed to the management of infections in women, and in particular the costs of managing the sequelae, mainly PID. Treatment of infections in women accounts for almost 80% of the total costs of treating *Chlamydia*. Whilst, the management of sequelae for uncomplicated, untreated infections *Chlamydia* accounts for 75% of the total costs.

Although this study demonstrates *Chlamydia* represents a significant economic burden, the actual figures are likely to be an underestimate of the full costs of managing *Chlamydia* and its sequelae. The authors used the lower range of estimates

of estimates for the direct healthcare costs of managing each of the *Chlamydia* and associated conditions. Secondly, the cost of managing complications in men (e.g. infertility and Reiter's syndrome) was excluded. Thirdly, infant costs exclude estimates for adverse pregnancy outcomes or mortality. Fourthly, costs of sequelae associated with asymptomatic infections were excluded even though upto 70% of infections in women and 30% in men are asymptomatic. Finally, the psychosocial costs of *Chlamydia* for patients, partners and the community were excluded.

Despite the exclusion of significant direct costs, Washington et. al. provide the current best estimates of the economic burden of *Chlamydia* in the U.S. Similar studies have not been conducted in the U.K or indeed in other English speaking countries.

4-3.2 Cost-effectiveness of screening strategies in women

Asymptomatic infections represent 70% of *C. trachomatis* infections in women and 30% of asymptomatic infections in men therefore it is vital to identify and treat these infections before further transmission takes place. Various methods for the detection of asymptomatic infections is currently available (see previous chapter). These methods include the use of different types of tests including culture tests and more recently, non-culture methods. Detection of asymptomatic *Chlamydia* infections is a function of type of test, levels of sensitivity and specificity for the diagnostic test used, type of population and the expected prevalence rate in the population to be screened. This section will review the cost-effectiveness of using different screening methods to detect *Chlamydia*infections in asymptomatic women.

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[4] Original values were updated using the US consumer price index (**Global Financial Data: http:**

In a US study, Phillips et. al. developed a decision analytic model to evaluate the clinical and economic implications of testing for cervical infection caused by *C. trachomatis* infection in all women attending routine gynaecologic visits (Phillips et. al. 1990). The authors compared a strategy of routine testing with cell culture or rapid tests (DFA or EIA) and a strategy of no routine screening. Different sets of assumptions were used for the characteristics of the diagnostic tests. The sensitivity of cervical swabs was assumed to equal between 70% and 80% and specificity of culture was assumed to equal 100%. Sensitivity and specificity for both the DFA & EIA tests were assumed to equal 60% and 98% respectively. The overall analysis revealed use of rapid tests followed by appropriate treatment in women with positive results would reduce overall costs where prevalence of *C. trachomatis* infection was 7% or more. When only direct costs are considered, the threshold value for rapid tests is a prevalence of 12%. The use of routine cultures would similarly reduce overall costs where prevalence of infection was 14% or greater. When only direct costs are considered, the threshold prevalence for culture is 25%. The authors conclude the choice of test should depend on the expected prevalence in the population, local costs and laboratory expertise. Marra et. al. have criticised this model for the high effectiveness used for tetracycline therapy. In addition to 90% efficacy for treatment, this model did not account for non-compliance of therapy.

Nettleman & Jones evaluated the cost effectiveness of screening for women at moderate risk (7.9%) for urogenital infections with *C. trachomatis* in a U.S population (Nettleman & Jones, 1988). This study evaluated the economic impact of direct costs only from a societal perspective. The study conducted in two parts is unique in that it incorporates both clinical and economic evaluations. The first part of the study was a clinical study of 434 sexually active college women to assess the sensitivity and

specificity of three serological tests, microimmunoflurorescence, indirect fluorescent antibody assay and an enzyme-linked immunoassay. The second part of the study design incorporated the development of a decision analytic model to evaluate the cost-effectiveness of the three screening strategies compared to a strategy of no screening. Unlike other studies, the authors developed a utility scale from 0 to 1, with 0 representing persistent infection (uncured) and 1 representing the absence of infection (cured). The cost-effectiveness of intervention was calculated by dividing the total cost by the utility score. The authors have used this methodology in other studies including research conducted during 1986 and 1991. Sensitivity and specificity of IFA were 87% and 64% respectively. Additional values for sensitivity and specificity of culture and direct antigen testing were derived from the literature. Effectiveness of antibiotic therapy was assumed to equal 90%, however, the authors did not specify the therapy used in the analysis.

The results of the modelling exercise demonstrated screening all women with a direct antigen test costing less than $12 (1987 values) was more cost-effective than a strategy of no screening and no treatment. However, this was achieved with a high rate of false negative results, with only 53% of women with true positive results. Thus, treatment would be provided unnecessarily. Culture tests either alone or as a confirmatory procedure was less cost-effective but had higher predictive values. Extensive sensitivity analysis revealed robustness of model for costs of tests, prevalence, complication rates for uncured infections and adverse events for antibiotic therapy.

In a study conducted in Sweden, Genc & Mardh, (1996) developed a decision analytic model to evaluate the use of tissue cell culture, confirmed enzyme immunoassay, and DNA amplification assays on either polymerase chain reaction or

ligase chain reaction. Treatment strategies used were doxycyline (7-day twice-daily oral taken at home) and azithromycin (1g single dose, oral) administered under supervision. Compliance rates were assumed to range between 50% and 90% for doxycyline, compliance with azithromycin, administered under supervision was assumed to be 100%. Efficacy for both regimens was assumed to range between 95% and 100%, with estimated cure rates of between 5% and 10%. The authors used two decision trees to track outcomes of screening women and of tracing and treating sexual contacts of women with a positive diagnosis of *C. trachomatis*. Probability estimates were obtained from published literature. The study evaluated both direct medical costs and indirect societal costs. All costs related to delivery of healthcare and those attributed to lost wages and lost productivity was obtained from published reports in Sweden.

The results of the modelling exercise demonstrated screening of women with any of the three diagnostic methods was cost-effective, when compared to no screening. DNA amplification combined with azithromycin treatment for patients with a positive test was the most cost-effective strategy, where prevalence of infection was at least 6%. Compared with no screening strategy, screening with enzyme immunoassay also generated savings and improved the cure rates but was less cost-effective than screening with DNA amplification. Compared with no screening, tissue culture is cost-effective only when the prevalence of infection is more than 14%. Compared to treatment with azithromycin, treatment with doxycyline resulted in significantly lower cure rates due to patients' poor compliance with twice-daily regimen for 7 days.

Trachtenberg et. al. developed a decision analytic model to evaluate the cost-effectiveness of screening using DFA compared to no screening in a cohort of 400k

women attending a state funded family clinic in California, for their annual Papanicolaou smear (Trachtenberg et. al. 1988). The study estimated direct costs only from the perspective of a third party payer. Assumptions used in the model included 90% sensitivity & 98% specificity for DFA test, a 9.8% baseline prevalence for *C. trachomatis* infection (high prevalence population), doxycyline 100mg orally twice daily for 7 days in positive patients + partners (95% effectiveness for drug). The model demonstrated 33 516 *C. trachomatis* infections would be eradicated, 8379 PID infections would be prevented, 335 cases ectopic pregnancy would 1760 cases of tubal infertility would be prevented, resulting in annual savings of US$13 million (1987 values). The authors conducted extensive sensitivity analysis to determine the effects of changing several of the key assumptions used in the model. The results demonstrated the model was robust for a range of values, which were deemed to be clinically relevant. The main disadvantage with this study was the exclusion of the economic impact of non-compliance of therapy with doxycycline and the use of medical charges as a proxy for costs.

A more recent study by Marazzo et. al. (1997) developed simple selective screening criteria for *Chlamydia*infection in women to evaluate the contribution of cervicitis to screening criteria and the cost-effectiveness of selective vs. universal screening. The design of the study was cross-sectional to assess 31 025 women in family practice and STD clinics in Washington, Oregon, Alaska and Idaho from 1989-1993. Different tests were evaluated according to where the women presented i.e. for women attending family clinics (11 141), a DFA test was used and for those women attending STD clinics (19 884),either a cell culture, DNA probe or EIA test was used for screening. The prevalence in this cohort of women was 6-6%. The study showed the independent predictors were: age <20 yrs, signs of cervicitis, new sexual partner,

multiple sexual partners and symptomatic partner. The risk factors were then used to develop selective screening criteria, which were applied to a hypothetical cohort of 1 million Family Planning and STD patients in a decision analytic model. Finally, the authors conducted an incremental cost-effectiveness analysis to compare universal, selective screening with DFA and no screening in the hypothetical cohort of women. The authors calculated both direct and indirect costs from a societal perspective in 1993 US dollars. Indirect costs were those attributable to loss of productivity as a result of *Chlamydia*infection. Intangible costs e.g. quality of life, pain , suffering were not included. The key assumptions used in the model included PID developed in 25% of untreated patients, DFA cost of $5, DFA sensitivity of 75%, treatment with doxycyline 100 mg orally twice daily, efficacy with doxycyline estimated to equal 95% and compliance rates with therapy of between 70% and 100%. A sensitivity analysis was conducted to establish the threshold values above which universal screening would achieve savings compared to selective screening. Selective screening was cost-effective in both cohorts of women, however in family planning clinics, universal screening prevented more *Chlamydia*cases than selective screening (47 025 vs. 44 674). However, this was at a higher cost thus selective screening nevertheless universal screening was deemed to be the preferred option by the authors. In the STD setting, selective screening was recommended. Sensitivity analysis showed the results of the analysis were robust with threshold values of 3.1% in family planning clinics and 6-9% in STD clinics. The use of a more expensive test e.g. LCR for screening had a minimal effect on the outcomes. The authors did not evaluate the effect of using azithromycin, a more expensive but more effective therapy.

In a Canadian study, Estany et. al. evaluated the cost effectiveness of different screening methods for early detection of *C. trachomatis* (Estany et. al. 1989). This

study compared the effectiveness of three different screening tests, traditional culture method with sensitivity of 73% and specificity of 99%, DFA with sensitivity of 70%, and specificity of 98% and thirdly enzyme immunoassay with a sensitivity of 60%, and specificity of 97%. The model was constructed such that all women with a positive test were treated with either tetracycline or doxycycline, efficacy assumed to be 95% and 100% respectively. Compliance rates for both regimens were assumed to be 70%. Literature was used to obtain complication rates for *C. trachomatis* infection and was similar to those used in other economic analyses. The study incorporated both direct medical and indirect societal costs. Direct costs were those incurred whilst testing, treating and managing costs of complications. Indirect costs were those associated with lost productivity of women as a result of *Chlamydia* and its sequelae. This study demonstrated both DFA and enzyme immunoassay tests for early detection were cost-effective in women where prevalence >6 or >7% respectively. Further, sensitivity analysis showed the probability of PID infection and cost of tests was the two variables, which affected the outcome of the model.

4-3.3 Cost-effectiveness of screening in pregnant women

Pregnant women are considered to be at high risk of *C. trachomatis*. The prevention of transmission to infants can result in the avoidance of additional costs incurred as a results of treating conjunctivitis and pneumonia in the babies. Additionally, prevention of transmission to the infant may result in lower mortality rates for new-borns.

Nettleman and Bell evaluated the cost-effectiveness of screening strategies in pregnant women for *C. trachomatis* from a third-party payer(Nettleman & Bell, 991). Screening and treatment strategies are more complex in pregnant women as treatment options are more limited, both mother and infant require therapy and sequelae for

infection are more varied. The authors compared the direct medical costs associated with culture in all patients, followed by treatment for positive results, DFA in all patients followed by treatment for positive cases or culture confirmation for positive DFA results and no screening tests. Prevalence in women was assumed to be 5%. Sensitivity for single cell culture method was 82% and specificity of 100%. In the case of DFA, sensitivity was assumed to equal 95% with specificity of 96%. Treatment regimen used in this model was erythromycin for 7 days. Treatment for a single sexual partner was also included in the analysis. If the cost of DFA was less then $US 6-30 (1990 values) or prevalence was > 6-1% in pregnant women, routine screening with DFA followed by treatment for positive results was the most cost-effective option. Where cost of DFA was < $US3.90 (1990 values) or the prevalence was higher than 6-7%, confirmation of a positive DFA results followed by treatment was the more cost-effective strategy. And if the prevalence of infection was > 14.8% or the cost of culture was less than $US7.50 (1990 values), culture followed by treatment for positive results was the preferred option. Where the mean cost of uncured infection was > US$284, DFA followed by treatment was the most cost-effective option. Sensitivity analysis demonstrated the variables affecting the outcome of results were prevalence of infection, cost of direct antigen test, cost of culture and mean cost of a persistent infection. The authors of this study concluded screening of pregnant women was not a cost-effective option in low prevalence populations (≤5%). The main disadvantage of this study was the use of charge data as a proxy for costs. However, it could be argued that from the perspective of the third-party payer, it is the charges, which they incur which represent real burden of infection with *C. trachomatis* according to the authors. Additionally, the authors did not allow for non-compliance of therapy with erythromycin in their estimation of efficacy of 92%.

4-3.4 Cost-effectiveness of screening strategies in adolescent males

Adolescent males have the highest rates of infection and associated complications than any other age groups (Washington, 1985, Stamm, 1984, Handsfield, 1986). Approximately 50% of non-gococcal urethritis infections are caused by *C. trachomatis* and a further 50% of cases of epididymitis are caused by *C. trachomatis* (Thompson & Washington, 1983). Epididymitis is a serious condition, which can lead to sterility. Further, this age group represents a major source of transmission to teenage girls.

Randolph & Washington (1991) evaluated the costs and benefits of screening tests for *Chlamydia* in adolescent males. The authors developed a decision analytic model to evaluate three screening methods in a hypothetical cohort of 1000 sexually active adolescent males. Screening methods evaluated in this study were leukocyte esterase urine dipstick with culture, with direct-smear fluorescent antibody (DFA) and with the option of no screening. The assumptions used for test sensitivity and specificity rates were taken from published literature. A conservative estimate of a 15% prevalence rate in this group was used for baseline analysis. An estimated 3% of patients in both the culture and DFA groups were assumed to be lost to follow-up. Patients in the leucoyte esterase group would not be lost to follow-up as the results are instantaneous. Efficacy for doxycyline 100 mg orally twice a day for 7 days was assumed to be 95% and the compliance rate was assumed to equal 65% thus overall effectiveness was estimated at 62%. The model considered direct medical costs only: treatment, screening, and complications in sexual partners, complications in infected men. The results showed leucokocyte esterase test had the lowest average cost-per-cure ($51) compared with direct-smear DFA ($192) and culture ($414). Compared with DFA, the authors estimated the leukocyte esterase test would save more than $9,

727 per cohort of 1,000 sexually active adolescent males, screened. The highest cure rates (56%) were achieved by the screening strategy although more costly. DFA achieved cure rates of 51%, LE test achieved cure rates of 49% and the no testing strategy achieved the lowest cure rates of 5%. A significant component of overall costs were those related to the treatment of infected female partners ($365 per infected case). Sensitivity analysis revealed robustness of model at clinically feasible values for major assumptions (prevalence, sensitivity, and specificity of tests, PID rates, and compliance, lost to follow-up rates). The sensitivity analysis demonstrated the leukocyte esterase test would result in lower cost-per-cure and lower overall costs, per cohort than culture and DFA at any prevalence of *C. trachomatis* infection. Compared to no screening, leukocyte esterase test would result in lower overall costs, per cohort at prevalence rates above 21%.

In an earlier study, Genc et. al. evaluated the cost-effectiveness of identifying asymptomatic carriers of *C. trachomatis* in a hypothetical cohort of 1000 adolescent males and their sexual partners/contacts (Genc et. al.1993). This study used a decision analytic model to evaluate the impact of using enzyme immunoassay on either leukocyte esterase for positive urine samples (LE-EIA strategy) or on all urine samples (EIA strategy), compared with no screening strategy. Additionally, the effects of confirming positive EIA results with a blocking assay were evaluated. Treatment regimens evaluated in the CEA were doxycyline, 100 mg orally twice a day for seven days and azithromycin, 1g orally single dose. Analysis was carried out with the aid of two decision trees, which demonstrated all possible outcomes for both adolescent males and their sexual contacts. Outcomes assessed were based on a range of values rather than discrete base case values. Sensitivity for EIA and LE tests were assumed to be 70-80% and specificity was assumed to be 75-85% and 95-100% respectively.

Follow-up rates were assumed to equal 90-97%, and cure rates of 97-100% in-patients who comply for both treatment regimens. Compliance for doxycycline was assumed to range between 50% and 100% and for azithromycin 100%. Additionally, spontaneous cure rate in untreated patients was between 5-10%. Males were assumed to disclose either 1 or 2 sexual partners and the follow-up rate for the partners was between 60-80%. Study evaluated both direct and indirect medical costs. Direct costs were those related to costs of samples, tests, counselling sessions, appointments and treatment of initial *C. trachomatis* infection and its sequelae for both index cases and their partners. Indirect costs were those related to lost productivity as a result of participating in a healthcare programme. Instead of using sensitivity analysis to test the robustness of the model, the authors used randomly selected probability and cost values chosen from a predefined range of values derived from spreadsheet simulations. Combinations of upto 1000 different variables were assessed to calculate outcomes of the decision analytic model. Results were expressed as 95% confidence intervals on the means of the results from all the computations.

The results showed, compared with no screening, the LE-EIA and EIA screening strategies reduced the overall costs where the prevalence of *Chlamydia* was more than 2% and 10% respectively. The EIA strategy improved overall cure rates by 12% but reduced the incremental savings by at least $2144 per cured male, compared with LE-EIA strategy. Confirmation of positive EIA tests reduced overall cost of the LE-EIA screening strategy where prevalence of *C. trachomatis* was less than 8%. In terms of antibiotic treatment, a single dose of azithromycin administered under supervision improved the cure rates of both screening strategies by 12-16% compared with a 7-day course of doxycyline whilst reducing overall costs by 5-9%. However, the authors thus making an economic comparison difficult did not provide the incremental

cost-effectiveness ratios for the treatment strategies. In summary DFA screening is cost effective in populations > 5% prevalence, although cell culture has a higher predictive value it is more costly. DNA amplification is more cost effective in populations with a prevalence of > 6% than other methods. The authors conclude use of LE-EIA screening in combination with treatment of positive cases with azithromycin was the most cost-effective strategy, however in low risk populations, positive EIA tests should be confirmed.

4-3.5 Cost-effectiveness of partner notification

This is a situation where a third party e.g. healthcare personnel take on the responsibility of informing the sexual partners of infected individuals and providing them with an evaluation of their exposure and treatment, if appropriate (MMWR, 1993). Katz et. al. (1988) have published results of two studies which have evaluated the cost-effectiveness of using field follow-up for patients identified as having *Chlamydia*infection as part of a screening process and female partners of men known to have had NGU. The authors developed a decision analytic model to evaluate the cost-effectiveness of different options. However they did not state the perspective adopted for analysis. The inclusion of direct costs only suggests the perspective of the STD clinic was adopted for the overall analysis. Costs for each strategy were determined from clinic personnel time, travel costs for healthcare personnel and other costs such as telephone calls made. A review of all resources used for 40 culture-positive patients was made to determine resource use. Medical costs were taken from those reported in published literature.

The first study was carried out in an STD setting where patients were assigned to receive empirical antibiotic therapy for *Chlamydia*infection or had

urethral/endocervical specimens cultured. The latter group of patients was asked to return in a week's time to obtain the results, if positive they were asked to return for a follow-up appointment. For those patients who did not return after two weeks, a letter was sent out advising them of the status of their culture and asked to make an appointment. The results of these groups of patients (3) were then compared with the results obtained from using field follow-up in another group of patients. In this study, field follow-up was defined as an extensive interview of the infected patient by a disease intervention specialist followed by contact using a step-wise approach (Marra, 1998). The results of the study showed that of 142 patients who had a positive *C. trachomatis* culture, approximately 34% (49) returned to obtain results and arrange a subsequent appointment. A total of 112 (79%) patients returned for treatment compared with 259/266 (97%) in the field follow-up group. The cost per patient of the field follow-up strategy was less than the reminder systems for both men and women.

In the second study, Katz et. al. compared the effectiveness of different methods for contacting females who were partners of men presenting with symptoms of NGU at an STD clinic. Over a six-month period, patients were randomised to receive counselling by a nurse for men to refer their sexual partners (n=217), interview strategy, counselling by a disease specialist who obtained names of sexual contact but did not attempt to contact them (n=240) and field follow-up where the sexual partner is informed (n=221). The results from the second study revealed a significantly larger number of treated partners per index case (0.72) than nursing referral (0.22) and the interview strategy (0.18; $p<0.001$ for both nursing and interview groups when compared with field follow-up). The lowest costs per patient were achieved for the field follow-up group, followed by nurse group and then the interview strategy group.

Univariate sensitivity analysis revealed both models were robust for costs of each strategy and the cost of untreated *Chlamydia*infection.

4-3.6 Cost-effectiveness of empirical vs. laboratory confirmed treatment

Nettleman (1986) used a predictive decision analytic model to evaluate the cost effectiveness of treating infected individuals who had a positive culture for *C. trachomatis* with those treated empirically i.e. based on signs and symptoms. Diagnostic tests used in this study was the cell culture method where spec = 99% and sensitivity = 90% for men and 66-88% in women. Prevalence in the various subgroups of patients were obtained from data on 22 063 patients who had attended an STD clinic in Indianapolis, USA between 1983-1984 and additionally from published literature. Patients were subgrouped according to high risk or low risk groups depending on their signs, symptoms and their history. Appropriate antibiotic treatment used in the model, was at that time, deemed to be tetracycline 2g/day for 7 days (newer therapies were not available). This analysis was conducted from a third party payer and thus only direct medical costs were evaluated. The results showed empirical treatment was the most cost-effective option for all patients attending the STD clinic. However, if this option was not feasible, the next best alternative was empirical treatment of high-risk women and culture-based therapy for low risk women. In men, the cost-effective option was that of empirical treatment in high-risk groups but in low risk males, performing no cultures and no therapy was the most cost-effective option.

4-3.7 Cost-effectiveness of treatment regimens

A number of different antibiotic treatment regimens are available for the treatment of *C. trachomatis* as outlined in the previous chapter. The availability of newer antibiotics

such as the fluoroquinonolone and azithromycin and cost containment measures by healthcare systems have led to research efforts to identify cost-effective treatment options. Newer drugs are more expensive than older, generic antibiotics however they may offer the advantages of fewer side-effects and increased compliance with therapy when compared to traditional treatment options (Hopkins, 1991; Bauchmann, 1996; Augenbraun, 1996). Nuovo et. al. (1995) evaluated the cost-effectiveness of five different antibiotics for the treatment of *C. trachomatis* in non-pregnant women from the perspective of a healthcare system in California (erythromycin, tetracycline, doxycyline, ofloxacin, and azithromycin). The authors developed a decision analytic model and based their estimates of probability values and costs on published literature, state health plan reports and health insurance companies. Extensive sensitivity analysis on the parameters, probability of PID infection and hospitalisation after treatment failure, cost of treatment for inpatient and outpatient PID and cost and efficacy of azithromycin and doxycyline. This model showed that the most cost-effective treatment strategies were the doxycyline and tetracycline strategies, followed by azithromycin, ofloxacin and erythromycin. In those patients who were non-compliant, azithromycin may be the best strategy because of the single dose, however, this was not accounted for in the analysis. Marra et. al. criticises this study for its simplistic model. Further sequelae beyond PID (e.g. chronic pelvic pain, infertility and ectopic pregnancy) were not considered in the analysis. Additionally, the authors did not include the impact of non-compliance with older treatment regimens on the overall cure rates nor the costs incurred in managing adverse drug reactions. This is particularly pertinent as some of the older treatments such as erythromycin and tetracycline have been shown to have higher adverse events compared to the newer

agents (Bowie, 1982; Hopkins, 1991). Costs of treating secondary transmission to sexual partners were not considered in the analysis.

Haddix et. al. (1995) also developed a decision analytic model to evaluate the cost-effectiveness of treatment regimens for uncomplicated infection with *Chlamydia*. The authors compared treatment with azithromycin 1g orally with doxycycline 100mg twice daily for 7 days in cohort of 10k non-pregnant women. Additionally, the authors evaluated the treatments based on two diagnostic strategies; laboratory confirmed *C. trachomatis* infection and presumptive diagnosis, based on clinical signs and symptoms. This study evaluated the economic impact from the perspective of the US healthcare system and for the publicly funded clinic. In the latter perspective, costs related to sequelae of infection would be managed in an out-patient basis. Probability estimates were obtained from published clinical trials. The effectiveness of doxycycline was adjusted for a compliance rate of 80%, and non-compliant patients were assumed to be treatment failures. For azithromycin, compliance was assumed to be 100% since it is a single dose regimen and was administered in the clinic. The costs included in the model were those relating to treatment, treatment of PID and its sequelae (chronic pelvic pain, ectopic pregnancy and infertility). Costs for sequelae, which would incur in future years were discounted at an annual rate of 5%. Costs relating to PID were taken from Washington & Katz (1991). Additionally, model assumed 25% of women with tubal-factor infertility would seek treatment. Sensitivity analysis was carried out for prevalence rate of infection in those women treated presumptively, doxycyline compliance rates, cost of PID and its sequelae, probabilities of developing PID in compliant and non-compliant patients and risk of developing further sequelae. The results from the healthcare payer perspective revealed used of azithromycin would cost an additional US$290k (1993 values) to treat *Chlamydia*infections in a cohort of 10k

women under a laboratory confirmed strategy, resulting in savings of US$1.2 million in the treatment of PID and its sequelae. This results in total savings of US$3502 per additional case of PID prevented. In the presumptively treated model, use of azithromycin would cost an additional US$ 290k and would save US$ 240k to treat a cohort of 10k women. This would result in incremental cost savings of US$800 per additional case of PID prevented for azithromycin versus doxycycline in treated patients. Extensive sensitivity analysis revealed the robustness of model to the extent that azithromycin achieved savings for all plausible values. However, the results of the presumptive model were more sensitive to changes in probability and cost estimates used in the model. From the perspective of the public health clinic, azithromycin would cost an additional US$ 220k (1993 values) for a cohort of 10k women in a laboratory-confirmed model, but would result in savings of US$ 29k from reduced treatment costs of PID. This would result in net savings of US$ 709 per additional case of PID prevented. In the presumptive treatment model, azithromycin treatment would cost an additional US$220k but would save US$5670 from reduced treatment costs of PID. This would result in net costs of US$ 3969 per additional cost of PID prevented. Sensitivity analysis for both strategies revealed that although azithromycin is not cost-effective under base-case assumptions, it becomes more cost-effective in public clinics with non-compliant populations and where prevalence of *C. trachomatis* infection is higher. The authors concluded that use of azithromycin is more cost-effective under laboratory confirmed conditions from the healthcare-system perspective. Azithromycin is cost-effective in the management of patients with for presumptive treatment resulting incremental cost savings of US$ 800 (1993 values) per case of PID prevented. Although, azithromycin is cost-effective, from the perspective of a publicly funded clinic, only a small percentage of treatment costs relating to PID and its sequelae is

incurred by the clinic thus this option is also more expensive. The remainder of the costs incurred in treatment of PID and other public or non-public organisations will absorb its sequelae, thus from a societal perspective, such savings are non-existent or artificial.

Marra et. al. (1997) further developed the models constructed by Haddix et. al. (1995) to evaluate the cost-effectiveness of azithromycin and doxycyline from the perspective of the Canadian healthcare system for a cohort of 5k non-pregnant women. The costs of managing complications of PID are lower in the Canadian system (justification used by Marra for developing this model). Probability estimates and costs for resources were obtained from the literature, hospital costing departments and expert opinion. The results revealed azithromycin in a laboratory confirmed model would result in saving of Can$ 279 150 (1995 values) for a cohort of 5k women. In the presumptively treated model, use of azithromycin would result in savings of Can$ 1700 for this cohort. In conclusion, Marra et. al. state that widespread use of azithromycin in Canada for laboratory confirmed cases of *C. trachomatis* would results in the avoidance of Can$3 million in direct medical expenses per year. However there are a number of limitations to studies conducted by both Haddix et. al. and Marra et. al. These include cost of managing adverse effects of antibiotic therapy were not included, cost of secondary transmission to sexual partners was not evaluated, different screening strategies were not evaluated and both models evaluate direct medical costs only thus the full economic impact from a societal perspective has not been evaluated.

Finally, Magid et. al. (1996) conducted an economic evaluation very similar to that of Haddix et. al. and also Marra et. al. in evaluating the impact of azithromycin compared to doxycyline in the treatment of women with *C. trachomatis* infection. The advantage of this study over the previous two studies is that it includes the impact of

adverse events related to treatment with antibiotics and the costing of sequelae which occur as a result of secondary transmission of infection. Additionally, Magid et. al. identified cure rates for different levels of non-compliance with doxycyline. The results of this study were similar to Haddix et. al. and Marra et. al. When base-case assumptions are used, azithromycin was the more cost-effective treatment option for uncomplicated *C. trachomatis* infection in women. Azithromyin resulted in a reduction in major complications of infection by 2392 compared to doxycyline at approximately 57% of the cost per patient. Nevertheless, the authors recognised that the higher initial cost of acquiring azithromycin may limit widespread use of this treatment option in an essentially fragmented healthcare system in North America.

4-3.8 Cost-benefit evaluation of a test-of-cure strategy

The value of routine tests after treatment of infection has been provided is unclear. Guidelines in the majority of countries do not recommend a test of cure although the majority of GUM physicians in Great Britain offer the service to patients (Radcliffe, 1990). In a Norwegian study (Schiotz & Csango, 1992) used a decision analytic model to evaluate the cost-benefit of a test-of-cure strategy in a hypothetical cohort of 10k women with a positive diagnosis of *C. trachomatis* infection. The tests used were either cell culture or a rapid test with a no test of cure strategy for those who failed initial therapy. In this model, patients were continually cycled until all patients achieved cured under the test-of-cure strategy. This study evaluated direct costs only, diagnostic tests, repeat physician visits, antibiotic therapy and treatment of sequelae. The analysis was conducted from a third party payer perspective. Antibiotic therapy used was lymecycline 100mg orally twice a day, a cheaper alternative to doxycycline at an assumed effectiveness of 95%. The results of the analysis demonstrated that the costs

of a test-of-cure strategy were approximately twice that of a no-test-of-cure strategy. Sensitivity analysis revealed the model was robust to changes in the sensitivity and specificity of tests used with assumed specificity of 98% and sensitivity of 80%, however this was dependent on estimates of the efficacy of lymecycline. However, non-compliance with therapy was not factored into the analysis. Additionally, costs of treating sexual partners, infants, male infertility and indirect costs associated with lost productivity as a result of test-of-cure were not incorporated in the analysis. The authors did not provide a definition of rapid tests used in the analysis. Although this study is titled 'cost-benefit-analysis, it does not attempt to value the benefits of testing the patients. Like the CDC, the authors recommended that a test of cure is not required. In those cases where a test of cure is required either for research or other purposes, authors Black (1997) and also Marra et. al. (1998) have recommended the use of cell culture methods due their lower positive predictive value in a treated population where prevalence is likely to be < 5%.

4-3.9 Summary of section

*Chlamydia*infections represent a significant economic burden. Asymptomatic infections account for between 30% and 70% of infections. Detection and appropriate management of asymptomatic infections may lead to a reduction in the total costs of treating *Chlamydia* and its sequelae. Women account for a significant component of the total costs of *Chlamydia*, and in particular the costs of complications such as PID. Additionally, adolescent males represent a high-risk population and a major source of transmission to young women. A variety of diagnostic tests are available for detection of asymptomatic infections. Economic evaluations conducted in this area suggest screening of asymptomatic individuals is a cost-effective strategy, particularly in

adolescent males and in young women. Further, treatment of *Chlamydia*infections with a single dose of azithromycin appears to be the most cost-effective treatment strategy. The extent of a reduction in societal costs is a function of the types of tests used and the expected prevalence in the population being screened.

Chapter Five

The Economic Burden Of *Chlamydia* In England And Wales

The previous chapter outlined the clinical features of *Chlamydia* and reviewed the economic literature in this area. Chapter four also identified the non-existence of published studies to evaluate the economic burden of *Chlamydia* in the U.K. The main objective of this chapter is to further the limited research conducted in this area by developing a cost of illness model to evaluate the economic burden in the UK. This chapter will utilise a variety of data sources to develop an economic model to evaluate the economic burden of *Chlamydia* and its sequelae.

The model will be developed in three main stages for England and Wales and to reflect the management of *Chlamydia* in primary care, specialist GUM clinics and general hospitals. This will be followed by the development of a model specifically for Scotland. Section 5-1 will provide an overview of the methodology for the development of the model. Section 5-2 will outline the development of the model for primary care and section 5-3 will outline the development of the model for GUM clinics. Section 5-4 will outline the economic model for general hospital admissions. Section 5-5 will evaluate costs associated with mortality due to complications of *Chlamydia*. The results and discussion of the complete model for England and Wales are presented in section 5-6. Section 5-7 will develop an economic model for Scotland in three main sections, primary care, GUM clinics and general hospitals. Sensitivity analysis of the key variables and assumptions used in the modelling will be tested for their variation on the results in section 5-8. Finally, a summary and conclusion to the chapter will be provided in section 5-9

Section 5-1

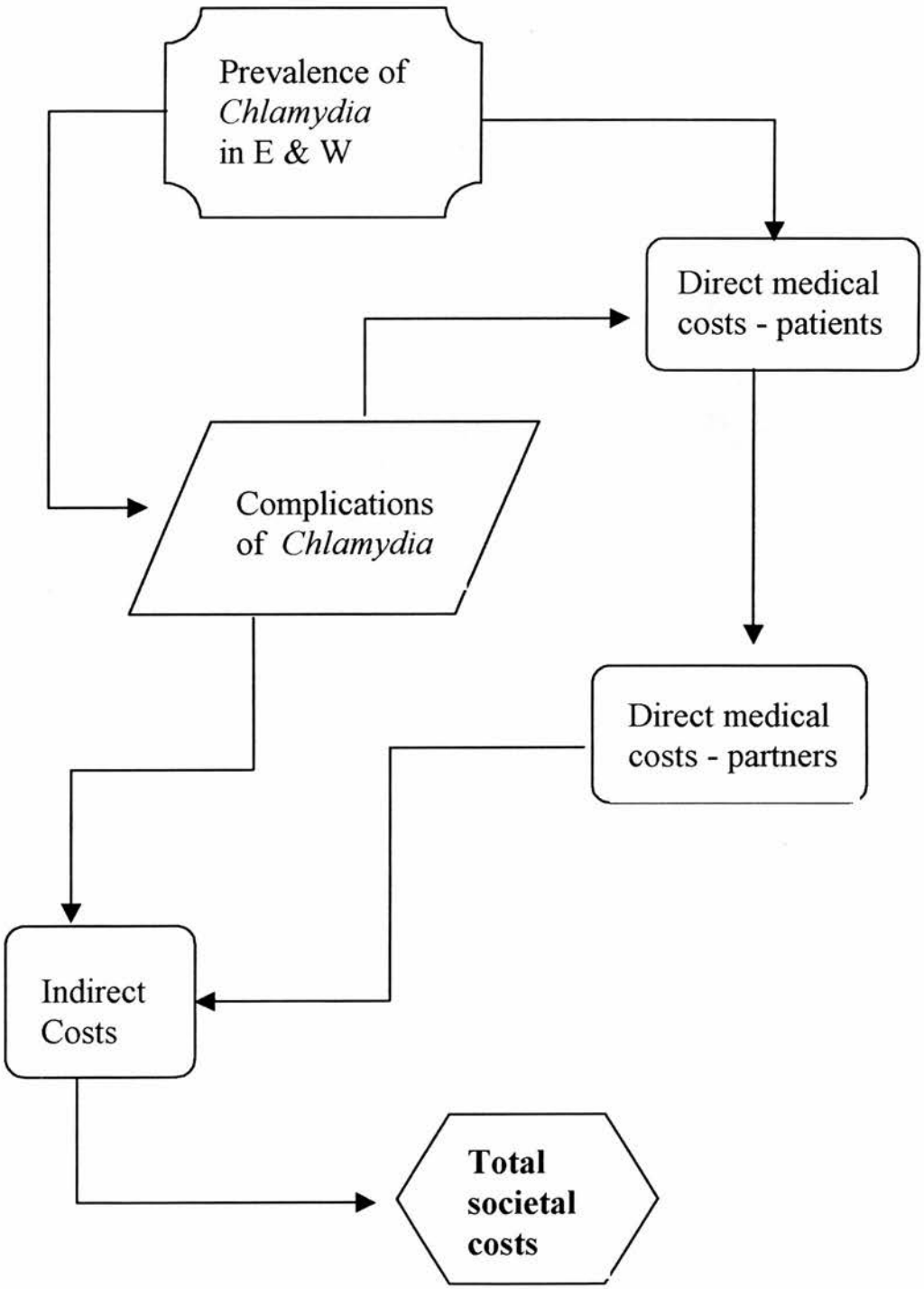
Methodology

The economic impact of *Chlamydia* from a societal perspective is evaluated using a prevalence-based approach to calculate the economic burden. This method involves the calculation of both direct and indirect costs for a group of patients in a given year. Direct costs are those costs incurred as a result of managing *Chlamydia* such as GP visits, hospital visits and pharmaceutical interventions. Indirect costs are those costs often referred to as opportunity costs, for example the loss of income or leisure time as a result of infection with *Chlamydia*. The framework for the economic model developed in this chapter is based primarily on research conducted in the U.S. In particular, the model developed by Washington et al. (1987) provides an excellent basis from which further research is elaborated upon. Figure 5.1 illustrates the economic costs of *Chlamydia* considered in this model.

Direct costs considered in this model include attendance for healthcare (GP visits, GUM clinic attendance, hospitalisation) and antibiotic treatment for both patients and partners. Reliable methods for estimated other healthcare costs such as health advisor, counselling and test-of-cure or follow-up visits were not available and are therefore excluded from this model.

Indirect costs considered in this model relate to lost productivity (either as a result of patients receiving healthcare such as attending GUM clinics or time required for rest and recuperation).

Figure 5.1: A cost of Illness model for Chlamydia trachomatis



The population considered in this model is those persons at highest risk for *Chlamydia*; the literature suggest this is primarily adults aged 16-44 yrs and infants who are particularly vulnerable for complications of *Chlamydia*, in the form of conjunctivitis. A number of routinely collected published data are used for epidemiology and resource utilisation associated with *Chlamydia* and its sequelae. Information relating to mortality rates attributed to the complications of *Chlamydia*, primarily pelvic inflammatory disease (PID) is also taken from aggregated data for England and Wales. The main advantage of this type of methodology is that it is appropriate for use with secondary data sources. The most comprehensive and reliable data on the incidence and prevalence of infection exists in the form of cases of infection reported to the public health laboratory services. The most recent analysis of this data exists for the year 1997, thus data from different sources will be standardised to the year 1999 which represents the base year for this model. Prevalence of infection can be identified through three key sources, primary care, hospital admissions and GUM clinics.

Section 5-2

Economic burden in Primary Care

5-2.1 Methodology

A prevalence based cost of illness model to estimate the economic burden of *Chlamydia* is adopted. The total number of consultations with General Practitioners is estimated, using ICD specific consultation rates for England and Wales. Published data on the frequency and quantity of resource utilisation associated with managing *Chlamydia* in primary care was not available. Thus, approximate resource utilisation for the study population was modelled to which standard published unit costs are applied.

The study population considered is those persons at high risk of infection; the literature supports considerations of adults aged 16-44 and infants aged less than 1. Prevalence data is determined from the Morbidity Survey in General Practice (1995) and updated to 1997 figures in order to standardise analysis for the overall economic model (see below). Although there is epidemiological evidence to support an increase in the prevalence and/or diagnoses of *Chlamydia* infections over recent years, this model adopts a conservative approach by assuming that rates of diagnoses in general practice have not increased since 1991/1992 and are therefore constant.

Direct costs in primary care relate to GP visits and drug treatment. It is assumed all patients diagnosed with *Chlamydia* in primary care will utilise one General Practitioner (GP) visit and receive one course of antibiotic treatment.

5-2.2 Morbidity Survey in General Practice (MSGP)

Estimates of the prevalence of *Chlamydia* and its sequelae in primary care are taken from the MSGP4, which provides data on consultations in primary care for the period 1st September 1991 to 31st August 1992. In this survey, the population base for the sample consisted of all doctors and nurses in 60 practices in England and Wales. Data captured relates to face-to-face consultations with patients on the NHS age/sex register (ASR) but does not include telephone contacts and private or temporary patients. A total of 502, 493 patients are included in the survey during the period 1 September 1991 to 31 August 1992. All diagnoses were coded according to the Read Clinical Classification System (method of classifying diagnoses developed by John Read for which the DoH purchased copyrights in March 1990). The Read classification is widely used in the NHS and by database providers such as General Practice Research Database (GPRD) and MediPlus™. The Read classification is a structured hierarchy of clinical and medical terms designed for use by clinicians. There are five levels within the Read system, with level 1 providing chapter headings and level 5 providing the maximum level of detail for the diagnosis. In comparison to the International Classification of Diseases (ICD) system, the Read system is more detailed. However, once the data is analysed by the office of national statistics formerly OPCS, the Read codes are translated into International Classification of Diseases, 9th revision. The main advantage of data used from this survey is that it is based on a large population sample size, 1% of England and Wales, with a reasonable geographical representation. However, the major disadvantages of this survey relate to the lack of randomisation for sample selection.

5-2.3 Definition of *Chlamydia*

Consultations for *Chlamydia* are categorised as those due to complicated *Chlamydia* and those attributed to uncomplicated *Chlamydia*. Uncomplicated *Chlamydia* is defined as other diseases of conjunctiva due to viruses and *Chlamydia* (ICD code 077), and other diseases due to viruses and *Chlamydiae* (ICD code 078). Complicated *Chlamydia* is defined as approximately half of the cases attributed to pelvic inflammatory disease (ICD codes 614-616), 1% of cases attributed to infertility (ICD code 628) and 43% of cases attributed to ectopic pregnancy (ICD code 633). Complicated *Chlamydia* in males is estimated to occur in 50% of cases identified as epididymitis/orchitis . In women, complicated *Chlamydia* is attributed to 30% of cases due to PID, 1% due to infertility and 1% due to ectopic pregnancy.

5-2.4 Estimates of Prevalence for *Chlamydia* in Primary Care

Prevalence is the level of presence of a disease during a given year and is defined as the number of persons who consulted at least once for a condition during the year. A person may contribute once to prevalence of a disease, but several times to the incidence of that disease if more than one episode of the disease is experienced through the year.

Prevalence of *Chlamydia* in primary care is estimated from rates of consultations with G.Ps resulting in a diagnosis of *Chlamydia*. Estimates of consultation rates using the ICD codes identified in the previous section were used for age groups (as defined in the MSGP4) for infants, 0-4 yrs and adults aged16-24yrs and 25-44 yrs for the period 1991-1992. In the base case analysis, it is assumed rates of consultations have remained constant. These rates of consultations were then extrapolated to the population at risk in 1999. Standard published data on population

were taken from an Office of National Statistics publication: Population trends, winter/1998 to which consultation rates from MSGP4 were applied. The calculations for extrapolation of consultation rates to obtain estimates of prevalence for *Chlamydia* in primary care is show below:

Example:

$$P = \frac{Co_{,\,a,s,\,icd} * Po_{\,a,s}}{10\,000} * Ch$$

P = Prevalence of *Chlamydia* in primary care
Co = Total consultations in primary care by age group, sex, and ICD code
Po = Population (age, sex)
Ch = percentage attributed to *Chlamydia* trachomatis

Such that males who present with a diagnostic ICD code 078 (oth diseases due to viruses and *Chlamydia*e), the consultation rate is 242 per 10k, the male population aged 16-24 in England and Wales is 2 921 000. All cases of ICD code 078 are attributable to *Chlamydia*. Thus the prevalence is estimated as follows:

$$P = \frac{242*2\,921\,000}{10\,000} * 100\%$$

Prevalence for ICD code 078 = 70 688

Thus, the prevalence for *Chlamydia* was estimated using all ICD codes relating to uncomplicated and complicated *Chlamydia* for males and females, the summary results are presented below (see appendix for detailed table of calculations)

Table 5.1 Prevalence of Chlamydia in primary care, England and Wales, 1999

	Male	Female	Total Prevalence
Uncomplicated *Chlamydia*	168, 387	211, 520	379, 908
Complicated *Chlamydia*	52, 514	199, 102	251, 616
Total	**220,, 901**	**410, 623**	**631, 523**

Thus, a total of 631, 523 consultations for *Chlamydia* are estimated for 1999. Of these, uncomplicated *Chlamydia* accounts for 60% of all consultations and females account for almost twice as many consultations compared to males.

5-2.5 Economic burden in primary care

5-2.5 (a) Direct costs

Direct costs of *Chlamydia* infections managed in primary care may be attributed to the management of both infected patients and their partners. The costs considered include GP visits and antibiotic prescriptions. This model assumes initial treatment is successful. Uncomplicated *Chlamydia* is assumed to result in 1 GP visit + 1 course of antibiotic treatment. Complicated *Chlamydia* is assumed to result in 2 GP visits and 2 courses of antibiotic. Cost estimates are taken from published data. The management of partners is estimated to result in one antibiotic prescription issued at the same time as the prescription for the diagnosed patient.

Costs were estimated by multiplying the prevalence of *Chlamydia*, as measured by the number of consultations in primary care by the cost of GP visits and antibiotic treatment. Costs were separated into those related to patients presenting in primary care and costs relating to the management of partners. This model assumes the cost of 1 GP visit and 1 course of antibiotic treatment for patients diagnosed with uncomplicated *Chlamydia*. Additionally, the cost of 1 course of antibiotic treatment is

assumed to apply to their partner. For complicated *Chlamydia*, the model assumes costs of 2 GP visits and one course of antibiotic treatment for patients and a further 1 antibiotic course of treatment for a partner. A G.P. consultation lasting 8.4 minutes is estimated to cost £15, and standard prescription charge of £5.40 is applied for the cost of antibiotic treatment (Netten & Dennet, 1998). In 1999, there were a total of 631,524 consultations due to *Chlamydia* infections diagnosed in primary care. Of these, 379, 908 consultations were due to uncomplicated *Chlamydia* and a further 251, 616 consultations were attributed to complicated *Chlamydia*. Table 5.2 below illustrates the direct costs of managing *Chlamydia* in primary care.

Table 5.2: Direct costs in primary care

Direct Medical Costs	Uncomplicated *Chlamydia* (£)	Complicated *Chlamydia* (£)	Total (£)
Patients			
GP visits (£15 per visit)	5,698,620	7,548,480	13,247,100
Antibiotic treatment (£5.40)	2,051,503	2,717,453	4,768,956
Partners			
Antibiotic treatment (£5.40)	2,051,503	1,358,726	3,410,230
Total Direct costs	9,801,626	11,624,659	21,426,286

Table 5.2 above illustrates the management of infections due to *Chlamydia* and its sequelae cost the NHS an estimated £21.4 million in 1999. Uncomplicated *Chlamydia* resulted in total costs of £9.8 million and uncomplicated *Chlamydia* contributed an estimated £11.6 million.

5-2.5 (b) Indirect costs

Indirect costs represent opportunity costs associated with a loss of productivity. This model estimates lost productivity for persons in employment. Estimates of the proportion of study persons in employment are based on figures obtained from the most recent census survey conducted in 1991.

The model assumes employment levels in 1997 are equivalent to rates obtained in the census survey. The figures were adjusted for gender, full-time and part-time employment. The model assumes attendance to consult a G.P for *Chlamydia* results in lost productivity. Uncomplicated *Chlamydia* is assumed to result in 1 lost day for full-time employees and ½ day for persons in part-time employment. Complicated *Chlamydia* is estimated to result in 2 lost days of productivity for persons in full-time employment and 1 lost day of productivity part-time employees. Finally, the model assumes average weekly earnings for full and part-time employees are equivalent.

Table 5. 3: Productivity loss in Primary Care

	Male (No days)	Female (No days)	Total (No days)
Uncomplicated *Chlamydia*	105,365	70,547	175,913
Complicated *Chlamydia*	69,783	194,212	263,995
Total productivity loss (number of days)	**175,148**	**264,759**	**439,907**

An estimated 440k days of productivity were lost in 1999 due to the management of both complicated and uncomplicated *Chlamydia* for cases diagnosed and managed in primary care (see appendix for further details of calculations).

Table 5. 4: Indirect costs in primary care

	Male	Female	Total cost (£)
Uncomplicated *Chlamydia* (£)	8,612,571	4,193,319	12,805,891
Complicated *Chlamydia* (£)	5,704,027	11,543,981	17,248,009
Total cost (£)	**14,316,599**	**15,737,301**	**30,053,900**

Table 5.4 above, illustrates the total indirect costs attributed to persons diagnosed with and managed for *Chlamydia* and its sequelae in primary care. Costs were estimated by multiplying the number of lost productivity days by the average daily earnings, £81.74

for males and £59.44 for females (New Earnings Survey, 1998). In 1997, indirect costs accounted for a total of £30 million. Of this amount, males and females accounted for roughly similar proportions, with indirect costs attributed to males totalling £14.3 million and £15.7 million for females.

5-2.5 (c) Results for costs of Chlamydia in Primary Care

Although, previous sections have outlined results of analysis for primary care, this section brings together the full analysis for both direct and indirect costs in primary care. The table below provides an illustration of total costs in primary care attributed to the management of *Chlamydia*.

Table 5.5: Economic Burden of Chlamydia in primary care

	Direct (£)	Indirect (£)	Total (£)
Uncomplicated	9,801,626	12805890.8	22,607,517
Complicated	11,624,659	17248008.76	28,872,668
All *Chlamydia*	21,426,286	30,053,900	51,480,185

From a societal perspective, the management of *Chlamydia* diagnosed in primary care is estimated to cost over £51.4 million in 1999. Direct costs account for approximately half the total costs. Uncomplicated *Chlamydia* is estimated to cost £32 million. Of this amount, direct costs accounted for £21.4 million (42%) of the costs and indirect costs accounted for the remaining £30 million (58%). Complicated *Chlamydia* is estimated to cost a total of £29 million.

5-2.6 Discussion of results for Primary Care

Direct costs considered in this model were restricted to GP visits and cost of antibiotic treatments. In reality, patients are likely to interact with other health professionals such as nurse advisors and psychologists. In addition, the cost neither of follow-up visits nor of diagnostic tests and procedures has been included in this model. The exclusion of these costs, due to the lack of available and reliable data is that the current model is likely to under-represent the true economic burden of *Chlamydia* in primary care.

The estimation of direct costs assumes all patients are in a stable, monogamous relationship and antibiotic treatment is prescribed for a single partner, however this is unlikely to be true for all patients. Additionally, this model assumes partners are not required to consult their G.P. In practice it is likely that at least some partners will either be required to consult or may feel that it is appropriate to do so. This assumption may result in an under-estimate of both direct and indirect costs.

The estimation of indirect costs assumes employment rates obtained from census data of 1991 are applicable to the population and economy of 1999. Clearly, rates of employment have fluctuated throughout the 1990's, however, the census data has been used as it is one of the most reliable sources of information available, by age group and gender. Secondly, weekly earnings are assumed to be equivalent for full and part-time employees. In reality this is unlikely to be true, thus this model provides a crude estimate of lost productivity. Finally, the use of average costs is also a crude estimate of the economic costs, whilst this is not ideal, it does nevertheless provide the reader with an estimate of the costs of *Chlamydia* in England and Wales.

Section 5-3

Economic burden in Genitourinary Medicine Clinics (GUM)

The previous section developed an economic model to capture direct and indirect costs associated with cases of *Chlamydia* diagnosed and managed in the primary care sector. In addition to presentation in primary care, cases of *Chlamydia* often present in specialist genitourinary medicine (GUM) clinics, without requiring referral from a G.P. This section of the chapter will further develop the economic model to capture direct and indirect costs associated with cases of *Chlamydia* managed in GUM clinics.

5-3.1 Methods

The prevalence of *Chlamydia* is obtained from published literature (see below). The base year for the development of this section of the model is 1999. Prevalence data reported in the literature refers to the year 1997 however it is assumed there has been no increase in the number of reported cases to GUM clinics for the year 1999. As with the previous section, due to a lack of reliable published data on resource utilisation for management of patients in GUM clinics, a series of assumptions is used to model the potential resource utilisation. Standard costs are then applied to the estimated resource utilisation in order to obtain direct and indirect costs.

5-3.2 Definitions

Diagnosis of *Chlamydia* are defined according to a set of national codes, KC60 (Sherrard, 1999) Uncomplicated *Chlamydia* is defined as diagnosis under the headings of C4A and C4C. Treatment of partners is defined as epidemiological treatment of suspected *Chlamydia*, code C4E. Complicated *Chlamydia* is defined using codes

C4B, *Chlamydia* opthalmia neonartum (C4D) uncomplicated non-gonococcal/non specific urethritis in males (C41), complicated NSGI (C5). Additionally, treatment of partners is captured as epidemiological treatment of NSGI (C41).

5-3.3 Prevalence in GUM clinics

The public health laboratory services Communicable Disease Surveillance Centre (CDSC) collate statistics from genitourinary medicine (GUM) clinics. In 1996, the Department of Health delegated the responsibility for the collation and analysis of this data to the CDSC. The most comprehensive data on the epidemiology of sexually transmitted infections (STIs) in England is available through KC60 forms. A national network of GUM clinics was created in response to the Venereal Disease Regulations (1916) when clinics have had a statutory obligation to report STI the Department of Health since 1919. Since then, the contents of the reportable cases have been revised on a number of occasions, most significantly in 1988 and 1995. The main disadvantage of KC60 data is that STIs diagnosed in other settings e.g. family planning clinics, termination of pregnancy clinics, antenatal care, well women clinics are not captured. The most recent data available is for the period 1997, however, this model assumes the number of cases reported in 1999 having not increased since 1997.

5-3.4 Direct costs

Direct costs considered in this model were restricted to outpatient attendance costs and antibiotic treatment for patients and partners. Costs relating to health advisors, counselling, patient follow-up and test of cure were excluded from this analysis. A total of 52, 734 cases of uncomplicated *Chlamydia* and 42, 303 cases of complicated

Chlamydia were reported to GUM clinics[5]. The direct costs were estimated by multiplying the total number of cases of *Chlamydia* by the associated resource utilisation, using the following assumptions:

Uncomplicated cases utilise 1 outpatient attendance
Complicated cases utilise 2 outpatient attendances and 1 inpatient attendance
Cost of outpatient visit = £65 (Netten & Dennet, 1998)
Cost of inpatient visit = £441 (Netten & Dennet, 1998)
Patients receive a single course of antibiotic treatment
One partner per patient receives a single course of antibiotic treatment
Cost of antibiotic treatment = £4.80 (standard prescription fee in 1997)

The table below illustrates the direct costs associated with managing *Chlamydia* in GUM clinics:

Table 5.6 Direct Costs of Chlamydia in GUM clinics

	Uncomplicated *Chlamydia*	Complicated *Chlamydia*	Total Costs
Outpatient attendance (£65)	3,427,710	2,749,663	6,177,373
In-patient attendance (£441)	N/A	18,655,403	18,655,403
Antibiotic treatment - patients (£5.40)	284,764	228,434	513,197
Antibiotic treatment - partners (£5.40)	284,764	228,434	513,197
Total direct costs (£)	**3,997,237**	**21,861,169**	**25,859,169**

Thus, the direct costs associated with management of *Chlamydia* in GUM clinics is estimated at £25.8 million, of which complicated *Chlamydia* accounted for approximately 85% of all costs.

5-3.5 Indirect costs associated with cases of *Chlamydia* reported to GUM clinics

Uncomplicated *Chlamydia* is assumed to result in lost productivity of 1 day (1 outpatient attendance) for full time employees and ½ a day for part-time employees. Complicated *Chlamydia* is estimated to result in lost productivity of 3 days for full

[5] Refer to appendix for details of calculations conducted for estimation of *Chlamydia* cases reported to GUM clinics

time employees (2 outpatient attendances and 1 inpatient attendance) and 1 ½ days for part-time employees.[6] The results of these calculations are shown in table 5.7 below.

Table 5.7 Indirect costs in GUM clinics

Total Indirect Costs			Total (£)
Uncomplicated	1,207,689	844,729	2,052,417
Complicated	4,256,621	1,073,982	5,330,603
Total Indirect Costs (£)	**5,464,310**	**1,918,711**	**7,383,020**

A total of 99 130 days of productivity were lost as a result of *Chlamydia* and its sequelae, approximately 66 850 days were attributed to male employees and 32 280 days were attributed to female employees. The economic loss totalled £7.3 million. Uncomplicated *Chlamydia* accounted for £2 million and complicated *Chlamydia* accounted for £5 million. Overall, males accounted for a much larger proportion of the total indirect costs.

5-3.5 Discussion of results for cases of *Chlamydia* reported to GUM clinics

Table 5.8 Economic burden of Chlamydia in GUM clinics

	Direct (£)	Indirect (£)	Total (£)
Uncomplicated	3,997,237	2052417	6,049,655
Complicated	21,861,932	5330603	27,192,535
Chlamydia (£)	**25,859,169**	**7,383,020**	**33,242,190**

The economic burden of *Chlamydia* in GUM clinics is an estimated £33 million per annum, of which approximately 78% are attributed to direct costs. Complicated *Chlamydia* accounts for 82% of the total costs. Males account for 55% of the cases of

[6] See appendix for details of calculations for estimation of productivity loss

Chlamydia reported to GUM clinics, however they account for 74% of the total costs. This is due primarily to a higher proportion of complicated cases of *Chlamydia* in males (67%). Complicated cases of *Chlamydia* in males occur concomitantly with other STIs. However, in females, complications of *Chlamydia* occur mainly in the form of PID, which is more likely to present in a general hospital setting. Whilst this reported data provides the most accurate information on prevalence of new cases of infection, it remains limited to GUM clinics. *Chlamydia* infections diagnosed in settings other than GUM clinics e.g. family planning clinics are not required to be reported to the Public Health Laboratory Services. Thus, these figures are likely to under-represent actual rates of prevalence.

Section 5-4

Economic impact of Hospital Admissions

The previous two sections have outlined the development of an economic model for cases of *Chlamydia* diagnosed in primary care and cases reported to GUM clinics. The majority of cases diagnosed in primary care are uncomplicated cases of *Chlamydia*. Complicated cases are most likely to present in the hospital sector. This section of the chapter will outline the development of the economic model for complicated cases of *Chlamydia* managed in general NHS hospitals.

5-4.1 Methods

As with the previous two sections, this component of the model is based on published literature. Published data is used to estimate prevalence of infection in England and Wales (see below). Hospital admissions for complicated cases of *Chlamydia* in females are considered in this analysis. Admissions are categorised as ordinary admissions (OA) and day cases (DC), however these data are not available by age group therefore estimates of OA and DC attributed to adults aged 15-44 yrs are estimated by extrapolating prevalence rates to age adjusted population for England and Wales. Finally, standard costs are applied to estimate levels of resource utilisation associated with complicated *Chlamydia*.

5-4.2 Definitions

Complicated *Chlamydia* is defined as conjunctivitis (ICD 233), salpingitis (ICD 371), PID (ICD 372) and infertility (ICD 376)

5-4.3 Hospital Episodes Statistics (HES)

Prevalence data was obtained from a publication titled 'Hospital Episodes Statistics' (HES) first introduced in April 1989. Statistics for English hospitals, in the form of finished consultant in-patient episodes (ordinary admissions and day cases) and unfinished episodes at 31st March '96. However, this data set excludes outpatient attendances. The first volume of data was published for 1988-89, and 2 volumes of HES data have been published for each year from 1988-89 to 94-95. The most recent data available relates to the financial year 1995-96 and is available in an electronic format on a CD. HES covers all medical specialities and includes private patients treated in NHS hospitals. HES records data as finished consultant episodes, which is defined as a period of care under one consultant, an unfinished consultant episode is where a patient is still occupying a hospital bed at the end of the year (HES, 1996).

5-4.4 Prevalence of *Chlamydia* infection in general hospitals

Estimates of the prevalence of infection with *Chlamydia* and its sequelae are based on identification of ICD codes for conjunctivitis, salpingitis, PID and infertility (see table below). The rates of prevalence were available in the format of combined ordinary admissions and day cases. The proportion of cases attributed to ordinary admissions and day cases was estimated by extrapolating the percentage of each type of case by age groups[7]. The table below illustrates the estimation prevalence of *Chlamydia* in the general hospitals:

[7] See appendix for detailed calculations

Table 5. 9: Prevalence in general hospitals, ordinary admissions and day cases combined

ICD		ordinary admissions & day cases combined by diagnoses		
		OA (mean duration)	DC	Total
233	Conjunctivitis	5 (5.1)	1	6
371	Salpingitis & oophoritis	847 (3.1)	138	985
372	Inflamm dis pelvic...	6177 (1.5)	1795	7972
376	Infertility, female	76 (1.5)	189	265
Total		**7104**	**2123**	**9227**

5-4.5 Direct Costs

Direct costs were estimated by multiplying the number of ordinary admissions, using mean number of days by the cost of a daily in-patient cost (£441) and the number of day cases by approximately half this amount (£220). Published estimates were not available therefore it was assumed a day case would cost 50% of an in-patient stay. In addition, it is assumed that all cases of ordinary admissions and day cases will incur the cost of 1 outpatient attendance (£65). The results are shown in table 5.10

Table 5.10 : Direct costs of Chlamydia in general hospitals

	Outpatient (£)	OA (£)	DC (£)	Total
Conjunctivitis	325	20066	220	20611
Salpingitis & oophoritis	55055	1904988	30360	1990403
Inflamm dis pelvic...	401505	8444577	394900	9240982
Infertility, female	4940	50274	2079440	2134654
Total	461,825	10,419,904	2,504,920	13,386,649

5-4.6 Indirect Costs

The indirect costs for patients admitted as either ordinary admissions or as day cases were estimated using a number of assumptions. Consideration of indirect costs was restricted to persons in employment, therefore all cases of conjunctivitis in infants are excluded. Day cases are estimated to result in 1 lost day of productivity for persons in full time employment and 1/2 day for persons in part time employment. Ordinary admissions result in a loss of the average number of days spent in hospital. Due to the

severity of cases presenting in general hospitals, it is assumed patients would require an additional five days for rest and recuperation for full time employees. In the case of part-time employees, only half the amount of productivity days is lost. Using census data, approximately 41% of females are estimated to be in full time employment and 17% in part-time employment. Cases of conjunctivitis for infants are excluded from calculation of indirect costs.

Table 5.11 Indirect costs for General Hospital admissions.

Hospital admissions	Productivity loss (days)	Total Cost (£)
Ordinary admission		
Salpingitis & oophoritis	4235	251703
Inflamm dis pelvic...	24767	1472132
Infertility, female	245	14534.86
	29246	1738370
Day cases		
Salpingitis & oophoritis	68	4060
Inflamm dis pelvic...	889	52814
Infertility, female	4679	278104
	5636	334979
Total (£)	**34881**	**2,073,348**

The above table illustrates there were a total of 34, 881 days of productivity loss as a result of cases of *Chlamydia* managed in general hospitals during the period 1994-1995 representing £2,073,348 (where the average daily earnings are £59.44). The calculations for estimating indirect costs is shown in appendix

5-4.7 Results for costs of *Chlamydia* in General hospitals

The table below summarises the results of direct and indirect costs from the previous two sections. Table 5.12 illustrates the economic burden of the management of *Chlamydia* in general hospitals.

Table 5.12 Economic burden of Chlamydia in General Hospitals, E& W

	Direct	Indirect	Total
Conjunctivitis	20611	N/A	20611
Salpingitis & oophoritis	1990403	255764	2246166
Inflamm dis pelvic...	9240982	1524945	10765927
Infertility, female	2134654	292639	2427293
Total	13,386,649	2,073,348	15459997

The economic burden of *Chlamydia* in general hospitals in England and Wales is estimated at £15.4 million. Approximately, 86% of the total costs is attributed to the direct costs of managing patients either as day cases or in-patients.

5-4.8 Discussion of results for General hospital admissions

The total economic burden of *Chlamydia* managed in general hospitals is estimated at £19.3 million. Direct cost account for the vast majority of total costs, approximately 89%. A major drawback of this analysis is the estimation of costs based on average duration of stays, for ordinary admissions. A more accurate analysis would utilise actual numbers of days per in-patient stay, however such data was unavailable. This criticism may also be applied to the use of average costs per inpatient stay and the assumption that day cases are equivalent in cost to one inpatient day. Similarly, these estimates were utilised in the absence of the availability of more detailed data.

The management of *Chlamydia* in general hospitals represents a significant economic burden. It is notable that cases of complications of *Chlamydia* in females present in general hospitals. There were no cases of *Chlamydia* or its sequelae identified in males.

5-5 Summary of Economic Burden in England & Wales

The economic burden of *Chlamydia* (excluding costs associated with mortality) in England and Wales is illustrated in table 5.13. The total cost of *Chlamydia* is estimated at over £100 million p.a. Direct costs account for £60.6 m representing 60% of the total costs. Indirect costs account for the remaining £39.5m. Within the different locations where *Chlamydia* presents, primary care accounts for more than half of the total direct and indirect costs, GUM clinics account for 36% of total costs and hospitals account for the remaining 16%. This study underlies the importance of the appropriate detection and management of *Chlamydia*, especially in the primary care sector.

Table 5.13 Economic burden of Chlamydia in England and Wales, excluding mortality

England and Wales	Direct (£)	Indirect (£)	Total costs (£)
Primary care	21426286	30053900	51480185
Hospital admissions	13386649	2073348	15459997
GUM clinics	25859169	7383020	33242190
Total costs (£)	**60,672,104**	**39,510,268**	**100,182,372**

Section 5-6

Costs attributed to Mortality associated with *Chlamydia*

The economic burden of *Chlamydia* would be incomplete without an estimate of the costs associated with early mortality as a result of *Chlamydia*. Thus, this section will attempt to evaluate these costs. Chlamydia is unlikely to result in mortality however complications such as PID which occur as a result of Chlamydia can result in mortality. Thus, this model will consider mortality due to pelvic inflammatory disease in women.

5-6.1 Methods

Cases of mortality attributed to PID were identified from standard mortality statistics published for England and Wales. It is assumed only 50% of cases, in women aged 15-45 yrs may be attributed to complications of *Chlamydia*. This model estimates lost productivity assuming women are productive until the age of retirement, 60yrs. The remaining working years are then multiplied by the average earnings. Calculations are estimated for women in both full and part time employment.

5-6.2 Results

There were a total of 68 cases of mortality attributed to PID. However, only 4 cases were in women aged 15-45 yrs. Thus, based on the assumptions outlined above, only 2 cases of mortality may be attributed to complications of *Chlamydia*.

Table 5.14: Indirect costs associated with mortality due to PID

	Min	Max	Mean
Full-time	£463,632	£1,390,896	£927,264
Part-time	£115,908	£347,724	£231,816
Mean	£289,770	£869,310	£579,540

Table 5.12 above illustrates the economic implications of early mortality in women with PID. The average economic loss is estimated at £579.5K where the remaining working age is taken as the mid-range between the minimum working number of years, 15 and the maximum number of working years, 45 from retirement age of 60yrs. The minimum economic loss is estimated at £289.7K and the maximum at £1.3 million.

5-6.3 Discussion

It has not been possible to ascertain the working status of cases of PID attributed to early mortality. Thus, this model assumes that all cases of mortality will be in paid employment until retirement age of 60yrs, however this may over-estimate the potential economic loss. Additionally, where women may not be in paid employment, there is an economic argument to value house-wives time at similar rates to average earnings. Whilst an over estimation of costs due to mortality is a possibility, this model attempts to minimise this impact by providing a range of potential values using a variety of different assumptions.

Section 5-7

Economic burden of *Chlamydia* in Scotland

A model to estimate the economic burden of *Chlamydia* in England and Wales was outlined in the preceding two sections of this chapter. The focus of this section is to develop a similar model to estimate the economic burden of *Chlamydia* in Scotland. As with the previous model, this model is divided into three main sections, Primary care, GUM clinics and General hospitals.

5-7.1 Primary Care

5-7.1 (a) direct costs

Data on the prevalence of *Chlamydia* in primary care were not available. It is therefore assumed that consultation rates obtained from England and Wales are directly applicable to the Scottish population. In 1997, there were an estimated 83 864 consultations due to *Chlamydia*[8]. Uncomplicated *Chlamydia* contributed 40 254 consultations and complicated *Chlamydia* contributed 43 610 consultations.

The direct costs considered include GP visits and antibiotic prescriptions for patients and partners. The table below illustrates the impact of direct cost for *Chlamydia* in Scotland.

[8] See appendix for detailed calculations

Table 5.15 Direct costs in primary care, Scotland

	Uncomplicated *Chlamydia* (£)	Complicated *Chlamydia* (£)	Total (£)
Patients			
GP visits	603810	1308300	1912110
Antibiotic Rx	217372	470988	688360
Direct costs	821182	1779288	2600470
Partners	217372	235494	452866
Total (£)	**1,038,553**	**2,014,782**	**3,053,335**

The direct cost of *Chlamydia* managed in the primary care sector is estimated at £3 million. Uncomplicated *Chlamydia* accounted for more than half of the total costs, at £2 million.

5-7.1(b) Indirect costs in primary care

Indirect costs were estimated on the basis of lost productivity as a result of *Chlamydia* diagnosed and managed in primary care. The proportion of estimated males and females in full time employment were assumed to lose 1 day of productivity for uncomplicated *Chlamydia* and 2 days of productivity for complicated *Chlamydia*. Persons in part-time employment were assumed to lose approximately half this amount of productivity. ½ day for uncomplicated *Chlamydia* and 1 day for complicated *Chlamydia*.

Table 5.16: Indirect costs for primary care, Scotland

	Male	Female	Total
Uncomplicated	543,608	460,081	1,003,689
Complicated	548,722	1,211,953	1,760,675
Total cost (£)	1,092,330	1,672,034	2,764,364

The table above illustrates the indirect costs attributed to the diagnosis and management of *Chlamydia* infections in primary care. An estimated £2.7 million

of lost productivity was due to *Chlamydia*. Uncomplicated *Chlamydia* resulted in lost productivity of £1 million and complicated *Chlamydia* resulted in lost productivity of £1.7 million.

5-7.2 GUM clinics

5-7.2 (a) Direct costs

In Scotland, the Inter Statistics Division (ISD) collates data on the number of cases of Chlamydia reported by GUM clinics. During the period 1998/99, there were a total of 2736 cases of *Chlamydia* reported by GUM clinics, of these approximately 1229 were in males and 1507 in females. However, it is not possible to differentiate between complicated and uncomplicated cases of *Chlamydia*. It is therefore assumed that the proportions of complicated and uncomplicated cases will be similar to those observed in England and Wales, thus:

- 46% of all cases reported for males are due to uncomplicated *Chlamydia*
- 67% of all cases reported for females are due to complicated *Chlamydia*

Estimations for direct costs are based on the following assumptions:

- Uncomplicated cases of *Chlamydia* are assumed to result in one outpatient attendance.
- Complicated cases of *Chlamydia* are assumed to result in two outpatient attendances.
- All cases and 1 partner are treated with a course of antibiotic treatment (assume standard prescription fee of £4.80)

The cost of an outpatient attendance is estimated at £65 (Netten & Dennet, 1998).

Table 5.17: Direct costs in GUM clinics, Scotland

	Uncomplicated	Complicated	Total Costs
Outpatient attendance (£65)	102,375	150,930	253,305
In-patient attendance (£441)	N/A	512,001	512,001
Antibiotic treatment - patients (£5.40)	8,505	6,269	14,774
Antibiotic treatment - partners (£5.40)	8,505	6,269	14,774
Total direct costs	**119,385**	**675,470**	**794,855**

The management of *Chlamydia* in GUM clinics is estimated to cost the Scottish health service approximately £794k p.a. Of this, uncomplicated *Chlamydia* accounted for £119k and the vast majority of the costs were due to complicated *Chlamydia* of £675k.

5-7.2 (b) Indirect costs

Indirect costs considered are estimated as loss of earnings as a result of diagnosis and management of *Chlamydia* for those persons in employment. Loss of earnings is adjusted for type of employment (full time or part-time) and gender. Uncomplicated *Chlamydia* is estimated to result in 1 day of lost productivity for full time employees and ½ day for part time employees. Complicated *Chlamydia* is estimated to result in a loss of 3 days of productivity for full time employees and 1 ½ days for persons in part-time employment.

Table 5.18 Indirect Costs in GUM clinics, Scotland

	Male (No days)	Cost (£)	Female (No days)	Cost (£)	Total (£)
Uncomplicated	347	28403	500	29717	58120
Complicated	1225	100138	738	43869	144007
Total	**1573**	**128541**	**1238**	**73586**	**202127**

The table above illustrates the indirect economic burden of *Chlamydia* GUM clinics. There were a total of 1573 days of productivity lost for males and 1238 days of lost productivity for females. When these figures are multiplied by the daily average earnings (£81.74 for males and £59.44 for females) these results in a cost of £202k. Uncomplicated *Chlamydia* accounts for 29% of the total indirect costs. Females account for a lower proportion than males, 36% vs. 64%.

5-7.3 General hospital admissions

5-7.3 (a) Direct costs

The prevalence of *Chlamydia* presenting in general hospitals in Scotland was not available from published sources, therefore the rates applying to England and Wales were extrapolated to the Scottish population (see Appendix for detailed calculations). The direct costs considered include both inpatient stays and day cases attributed to cases of complicated *Chlamydia* in women. Ordinary admissions and day cases are assumed to cost £441 per day. The total direct cost impact of *Chlamydia* managed in general admissions is illustrated in the table below.

Table 5.19 Direct costs in General hospitals, Scotland

Cost estimates	OA	DC	Total
Conjunctivitis	200170	6174	206344
Salpingitis & oophoritis	885881	82908	968789
Inflamm dis pelvic...	5292	437031	442323
Infertility, female	0	0	0
Direct costs	**1091343**	**526113**	**1617456**

Table 5.19 above illustrates the impact of direct costs for cases of complicated *Chlamydia* managed in general hospitals. Using population estimates of 1997, *Chlamydia* cost an estimated £1.6 million in direct costs in Scotland. Approximately, £1 million was attributed to admissions and the remaining £0.5 million was due to day cases.

5-7.3 (b) Indirect costs

The indirect costs for patients admitted as either ordinary admissions or as day cases were estimated using a number of assumptions. Indirect costs are considered for persons in employment. Thus cases of conjunctivitis in infants are excluded. Day cases are estimated to result in 1 lost day of productivity for persons in full time employment and 1/2 day for persons in part time employment. Ordinary admissions result in a loss of the average number of days spent in hospital and an additional five days for rest and recuperation for full time employees. In 1997, there were an estimated 1million females aged 15-44 yrs. In the case of part-time employees, only half the amounts of productivity days are lost. Using census data, approximately 41% of females are estimated to be in full time employment and 17% in part-time employment. Cases of conjunctivitis for infants are excluded from calculation of indirect costs. Details of the estimation of productivity days lost may be found in the appendix.

A total of 3657 days of productivity were lost for the management of *Chlamydia* in general hospitals. All cases of lost productivity were in females, where a total of 3657 days of productivity were lost for persons in full and part time employment. This results in total indirect costs of £217, 380 where the average daily earnings for females are assumed to equal £59.44.

Section 5-8

Summary of Results of the economic burden of *Chlamydia* in UK

In 1999, the total economic burden of *Chlamydia* in England and Wales was an estimated £108 million. Direct costs accounted for £65.3 million and indirect costs accounted for £43 million. Primary care represents the largest proportion of both direct and indirect costs, with direct costs accounting for £24 million and indirect costs accounting for £33 million. The next largest cost burden was borne by GUM clinics where £25.8 million was attributed to direct costs and a further £7.5 million attributed to indirect costs.

Table 5.20 Summary of results for UK

	Direct	Indirect	Total
Primary care	24479621	33167397	57647018
Hospital admissions	15004105	2290728	17294833
GUM clinics	25873944	7585148	33459091
Total costs	**65,357,669**	**43,043,273**	**108,400,942**

Section 5-9

Discussion and conclusions to Chapter

This cost of illness model clearly demonstrates the significant economic burden due to *Chlamydia trachomatis* in Great Britain. However, these estimations represent conservative figures due to a number of reasons. The key to this analysis is the number of persons with asymptomatic infections. Whilst, this variable was tested in a sensitivity analysis, the main study underestimates the likely prevalence rates and subsequent economic impact. The model utilises data from primary care, secondary care and GUM clinics only. Whilst these settings are likely to capture the vast majority of *Chlamydia* infections, there remain a number of other parts within the NHS where infections may present but will not be captured in the statistics used in this model e.g. antenatal clinics, gynaecology units, family planning clinics and abortion clinics. Indeed, the extent to which the sectors of the NHS included in this model represent the vast majority of infections is difficult to determine. Given that the prevalence of infection particularly in abortion clinics and family planning clinics is higher than in the normal population, this model underestimates the economic burden due to *Chlamydia*. The figures for costs represent the lower range of unit costs associated with each *Chlamydia* condition. Costs due to PID are based on average hospital admission costs and do not capture costs associated with infertility or ectopic pregnancies. The exclusion of such costs is due to lack of reliable incidence, prevalence and cost data from the available literature. Costs associated with infertility and Reiter's syndrome in men was not estimated. Costs associated with epididymitis in men not in the age range 16-44 no in post-gonococcal urethritis in men. Infant

costs due to adverse pregnancy outcomes or neonatal mortality are not estimated. Intangible costs due to the *Chlamydia* infection not estimated due to difficulties of quantifying.

The results of this study cannot be compared to other studies conducted in the U.K as this is, to the author's knowledge, the first study to estimate the economic burden of *Chlamydia* in the U.K. Whilst studies conducted in other healthcare systems may not reflect similar patterns of management, it is nevertheless, of interest to note that the results reported in this chapter are remarkable consistent with the findings of a landmark study conducted by Washington et. al. in the U.S population. According to their study infections in women account for 79% of total costs. In addition, 75% of the costs may be attributed to management of the complications of untreated infections. Direct costs account for 51.4% of the total. A remarkably similar estimate is provided by the cost of illness study for England, Wales and Scotland, with direct costs accounting for 54% of the total. However, in this study complications of *Chlamydia* accounted for only 18% of total costs as it was assumed complications would present in secondary care only, in the form of hospital admissions. Women accounted for all costs related to management of *Chlamydia* in general hospitals.

The methodology used for the cost of illness study is based on the prevalence approach and as such the economic burden for *Chlamydia* is estimated for a given year only. Since a large proportion of infections remain asymptomatic, the subsequent complications may not be apparent until future time periods. In addition, there remains controversy over the methodology of economic evaluations with particular reference to the type of costs, which should be

considered, and the methods for costing resource utilisation. However, it is not the focus of this thesis to provide a comprehensive overview of this area. Whilst the author accepts there exists controversy in the methodology of cost of illness studies, the aim of this research has been to provide as comprehensive and realistic an estimate of the total societal burden of *Chlamydia*. Whilst there remain a number of caveats to this evaluation, the model provides a reasonably accurate estimation of the economic burden of *Chlamydia* in England, Wales and Scotland, hitherto unavailable.

This chapter has provided a detailed analysis of the economic burden of *Chlamydia* and evaluated the impact in terms of the areas of the NHS where cases are likely to present, in primary care, secondary care and GUM clinics. The management of *Chlamydia* has long been understood to be less than optimal, both from a clinical and an economic perspective. These economic findings of this study serve to illustrate the public health importance of detecting and managing this infection appropriately from a societal perspective through the use of effective prevention and control programmes.

CHAPTER SIX

A Decision Analytic Model to Evaluate cost effectiveness of Antibiotic Treatment for Women Diagnosed with *Chlamydia trachomatis*

The economic burden of *Chlamydia* in the U.K is in excess of £126m. Whilst a large proportion of these costs may be unavoidable, a significant proportion of costs, in particular those attributed the complications of *Chlamydia* may be averted by identifying and treating infections appropriately. Thus, the focus of this chapter will be to apply the theory of decision analysis to the management of *Chlamydia* specifically for identifying optimal treatment strategies.

6-1 Methods

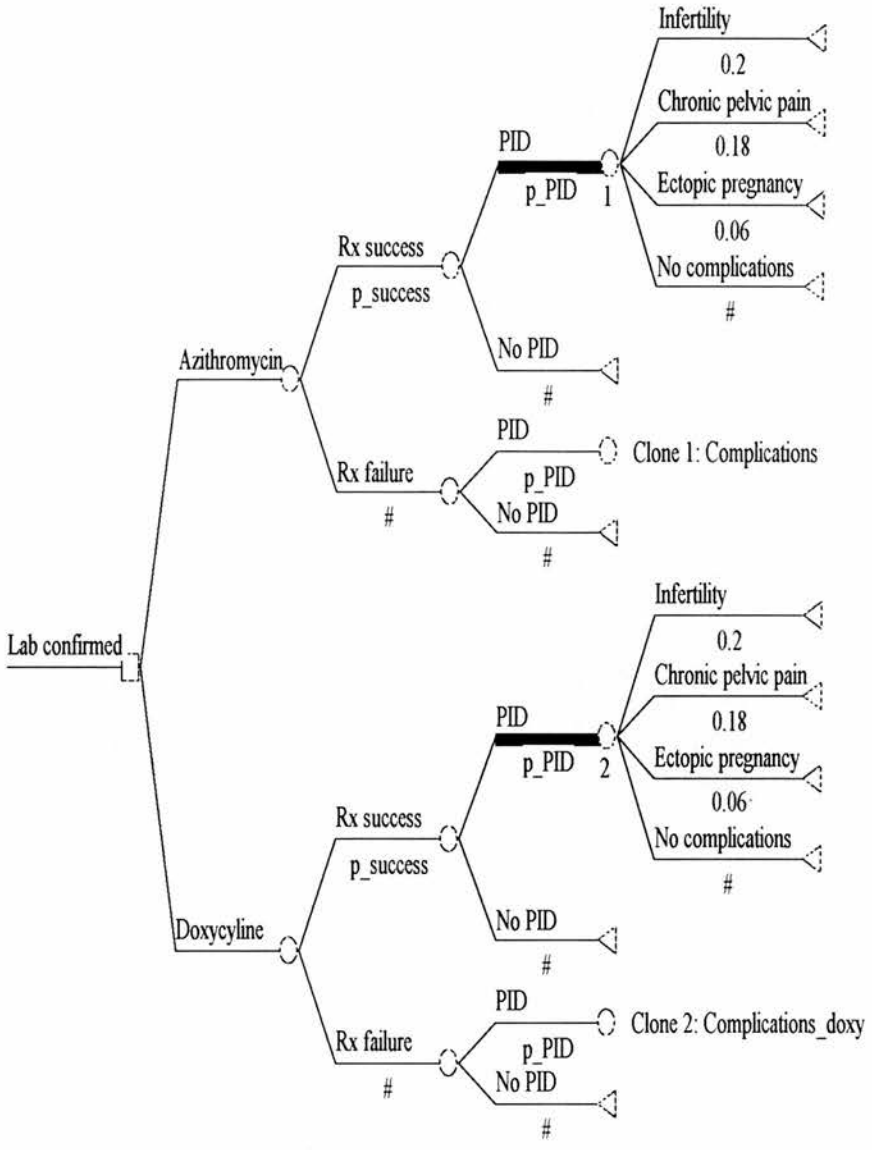
An economic model to evaluate cost effectiveness of two antibiotic treatments. The model is based on and developed from a review of the available literature. A Medline search of the English language literature from 1979 to 1999 with the key words "cervicitis," "*C. trachomatis*," "pelvic inflammatory disease," "economic cost," "azithromycin," and "doxycycline," was conducted. Eligible studies included all published randomised controlled trials of non-duplicated data in which a study antibiotic was used to treat *C. trachomatis* at doses consistent with UK or CDC guidelines. Studies excluded from the analysis were uncontrolled clinical trials, case series, and interim studies with data included in later reports. In addition, the reference list for each of the included studies was examined to identify further studies.

This search led to the identification of a number of articles. Additional literature was augmented through manual searches of references listed in key articles. The model was developed using a computer software package, DATA™ (version 3.5 for health care).

6-2 Decision tree

Figure 6.1 displays the decision model used in this analysis. The model was developed for a cohort of women diagnosed with uncomplicated Chlamydia trachomatis. The clinical pathway for uncomplicated *Chlamydia* is based on a thorough review of the literature. Whilst figure 6.1 does not reflect all aspects of clinical care and outcomes, the model attempts to characterise the important uncertain outcomes and probabilities. For simplicity, this model evaluates treatment on the basis of a confirmed infection through appropriate screening and detection methods. Once an infection has been confirmed, the model assumes treatment with either azithromycin or doxycyline is prescribed. The choice of treatment regimens to be evaluated in this model has been restricted to those where comparative efficacy data, derived from multinational trials is available in the published literature. Once treatment has been prescribed, the effectiveness of the regimen is a function of both the clinical efficacy and compliance with treatment. Where infection is successfully cured, the branches PID, infertility and ectopic pregnancy illustrate the probability of developing complications. For simplicity, the analysis is restricted to evaluation of two drug treatments, azithromycin, as this has consistently been demonstrated to be a cost-effective option and doxycyline, a widely used antibiotic in the UK

Figure 6.1: a decision analytic model to evaluate cost effectiveness of azithromycin and doxycyline in the treatment of uncomplicated Chlamydia trachomatis



6-3 Probability estimates

The model is used to evaluate the efficacy of each treatment option in curing an uncomplicated *C. trachomatis* infection and in preventing subsequent PID. The probability estimates for each treatment option were derived from previously published literature. A Medline search of the English language literature from

1979 to 2000 using the MeSH headings "cervicitis," "*C. trachomatis*," "pelvic inflammatory disease," "economic cost," "azithromycin" and "doxycycline," was performed. The literature was used to determine the probability of curing infection with each treatment option and the probability of major and minor side effects for each agent. The model assumed side-effects of treatments was equivalent and was excluded from the analysis.

The probability estimates of failure to respond to initial therapy were also derived from the published literature. Probability estimates were identified for the subsequent development of PID or requirement for hospitalisation in patients who fail initial therapy. Estimates for probabilities were based on published literature obtained from a Medline search of epidemiological data on acute PID including information on hospitalisations. (Nuove et. al. identified 6 reports).

Table 6.1: Key findings of selected comparative studies to evaluate efficacy of azithromycin and doxycyline in the treatment of C. trachomatis infection

Author	Patients (n)	Population	Key findings
Hammerschlag et. al. 1993	73	Adolescents (*Chlamydia*-positive)	Azithromycin – 100% efficacy Doxycyline – 92.9% efficacy
Ossewaarde et. al. 1992	60	Females (asymptomatic)	Azithromycin - 100% Doxycycline – 100%
Steingrimsson et. al. 1990	182	181 Males (symptomatic)	Azithromycin – 97.7% Doxycyline – 97.9%
Martin et. al. 1992	457	Persons ≥ 16yrs (symptomatic)	Azithromycin – 96.4% Doxycyline – 97.6.%
Thorpe et. al. 1996	597	Persons ≥ 15yrs (symptomatic)	Azithromycin – 97.4% Doxycyline – 98.7%
Lassus, A. 1990	108	Persons > 18 (symptomatic)	Azithromycin –100% Doxycyline – 100%

Azithromycin – 1g stat.
Doxycyline – 100mg bd for 7 days

Table 6.2: Key findings of selected studies on compliance with anti-Chlamydia therapy

Author	Patients (n)	Population	Key findings
Augenbraun et. al.	109	Symptomatic patients + contacts	Therapy – doxycycline 30% compliance rate
Katz et. al. 1992	406	Symptomatic patients + contacts	tetracycline, 500mg 4 times daily 71.4% of males compliant 62.2% of females compliant

Table 6.3: Key findings from selected studies on Pelvic Inflammatory Disease & its sequelae

Author	Patients (n)	Population	Key findings
Stamm, 1984	246 females	Diagnosed patients	Post treatment PID morbidity in 7/70 women (10%)
Jones et. al. 1986	60 females	symptomatic for *C. trachomatis*	No women developed PID post-treatment
Westrom, 1980	1000	Cohort of U.S women	Ectopic pregnancy post PID =5.7% Infertility post PID = 20.6%
Westrom, 1992	2501	Symptomatic of PID	Infertility rate = 16% Vs 2.5% in control group

Wherever possible conservative probability estimates were used in the model (see table below)

6.4: Probability estimates used in model

Variable	Base case
Efficacy	
Azithromycin	0.96
Doxycyline	0.96
Compliance	
Azithromycin	1.0
Doxycyline	0.8
PID	
After success	0.06
After failure	0.2
In-patient treatment	0.14
Out-patient treatment	0.86
Sequelae	
Chronic pelvic pain	0.18
Ectopic pregnancy	0.06
Infertility	0.2
Chlamydia infection	0.2

Sources: Marra et. al. 1995 and references listed in tables 6.1-6.4

6-4 Estimates of costs

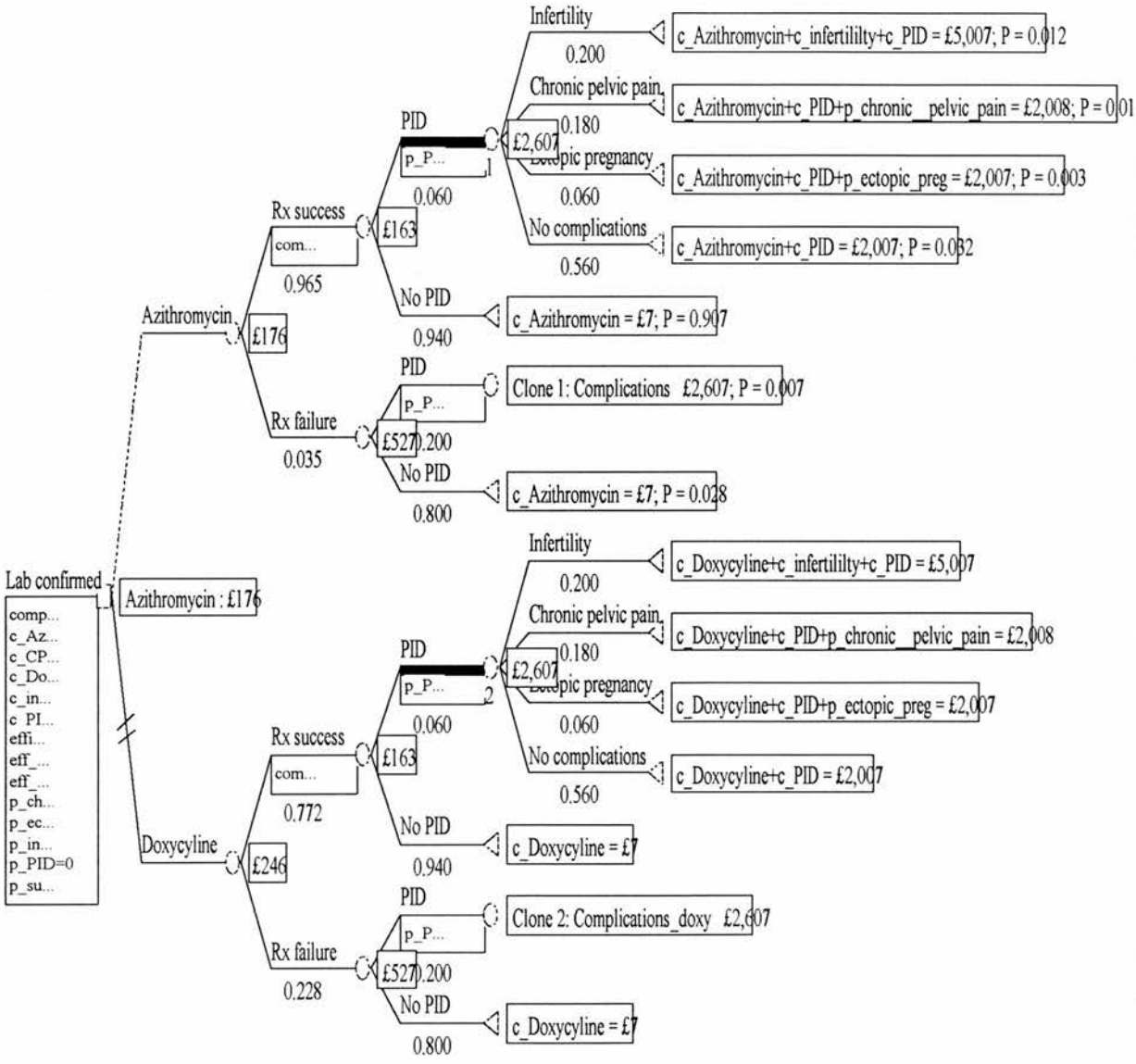
The model evaluates direct costs of uncomplicated *Chlamydia* and its sequelae and does not incorporate indirect or intangible costs. The published data on the utilisation of resources associated with most medical conditions in the UK, is at best sparse. In the case of uncomplicated *Chlamydia*, there is no detailed information available. Therefore, in order to estimate the potential cost implications, resource utilisation has been modelled as follows.

It is assumed PID cases utilise an average of 5 in-patient nights and 2 out-patient attendances. Similarly, chronic pelvic pain is assumed to result in the utilisation of 3 in-patient nights and 2 outpatient attendances. Infertility is estimated to result in the use of 1 course of fertility treatment. The cost of all resources was obtained from the published literature, with the exception of fertility treatment (personal correspondence with Oxford Health Trust).

6-5 Results

Figure 6.2 illustrates the decision model, including the main results (rolled back). The model illustrates, azithromycin should be the antibiotic regimen of choice with an expected cost per cure of £176 vs. £246 for doxycyline.

Figure 6.2: Rolled back Decision analysis model of azithromycin and doxycline



6-6 Discussion

The main disadvantage of this analysis is the lack of any real-life data hence the reliance on estimates of probability values obtained from the literature. In addition, in the absence of real cost data, economic costs have been modelled. The outcome of interest chosen for this analysis was the cost per cure. This outcome represents the primary interest from both a clinician's and patient's perspective. Estimates for the probability values were obtained from the literature, ideally, these values should be obtained either from clinical or real-life studies. However, the analysis aimed, whenever possible, to use conservative estimates. In particular, compliance rates for doxycyline are assumed to equal 80% although the literature reports figures as low as 50%. Treatment with azithromycin can be safely assumed to equate to 100%, for a single dose. Despite this disparity in effectiveness and the relatively high cost of azithromycin, treatment with the latter has been shown to be cost effective.

CHAPTER SEVEN

An Econometric Model for Selection and Screening of Patients with Suspected *Chlamydia*

The previous chapter illustrated the principles of applying decision analysis to the management of *Chlamydia*. The model demonstrated that in those individuals who are screened for *Chlamydia* and test positive, the most cost-effective treatment option is a single dose of azithromycin, 1g stat. However, one of the most difficult issues is identifying asymptomatic individuals at risk of infection screened. There is currently a dearth of literature on a comprehensive set of risk factors. In the U.S, studies of sexually active females presenting for screening during visits to healthcare providers suggest that age is the strongest of the socio-demographic factors associated with infection (MMWR, 1993). However, the precise contribution of each risk factor is unknown. Nevertheless, selective screening of individuals has been advocated as a potentially effective measure for identifying asymptomatic infections. Whilst studies have been conducted to determine whether a set of clinical, behavioural and demographic characteristics may be used to identify women at high risk of *Chlamydia*, few have attempted to quantify the contribution of risk factors.

This chapter will therefore seek to advance the research in this area by attempting to quantify the contribution of a variety of risk factors for infection with *Chlamydia* trachomatis.

7-1 Introduction

Routine screening for *Chlamydia* is not yet widely available. In the absence of screening, a number of risk factors known to be associated with *Chlamydia* infection are often used to determine whether treatment should be offered to individuals. Recognised risk indicators for *C. trachomatis* infection include multiple sexual partners, young age, use of non-barrier contraceptives and concomitant STD(Rietmeijer, C. 1991, Pearlan & McNeeley, 1992)

Stergachis et. al. (1993) conducted a study of women aged between 15-34 yrs to identify risk factors for *C. trachomatis* infection. A population based sample of asymptomatic women attending two primary care clinics in Seattle was included in the study. *C. trachomatis* was isolated from 67 of 1804 women (3.7%). A step-wise multivariate regression analysis demonstrated, seven of the characteristics were independently associated with infection; unmarried, symptoms of cervical ectopy, black race, douching, nulliparity, age < 24 yrs and two or more partners in the preceding year.

Karam et. al. conducted a study of asymptomatic males presenting in an emergency room at New Orleans Hospital, U.S. (1986). There were 85 eligible patients who participated in the study. The results demonstrated age (<26yrs), history of gonorrhoea and number of sexual partners (>4) in previous year were all statistically significantly shown to be related to presence of *C. trachomatis* infection. Other factors such as race, marital status, age at first intercourse and upto 4 partners in previous year were not statistically significant.

7-2 Methods

During the period 1997-1998, a sample of 491 consecutive patients presenting at St George's Hospital, London were asked to complete a self-administered questionnaire designed to capture information patient demographics, behavioural and clinical signs and symptoms.

A questionnaire was developed in order to facilitate the collection of data to identify a variety of factors that may be important in identifying women at high risk of infection. The underlying basis for the identification of factors, which were included in the questionnaire, was a comprehensive literature review of potential risk factors for *Chlamydia* trachomatis. A wide range of variables has been identified as potential risk factors for infection with *Chlamydia*. These variables are grouped as patient demographics, behavioural and clinical signs. Patient demographics are represented by variables such as age, marital status, race and education. Behavioural variables include age at first sexual intercourse, type and use of contraceptive methods, number of sexual partners and history of sexually transmitted diseases. The clinical signs and symptoms include those noted by the doctor or patient such as ectopy, contact bleeding, pain when passing urine, pain in lower abdomen and partners with any symptoms.

In order to evaluate whether the presence of *Chlamydia* infection is a function of the characteristics and behaviours of the patient, a binomial regression model was developed. The theory underlying binomial models and their applicability has been covered extensively in the literature. The binomial regression model is based on the logistic cumulative distribution function (c.d.f.) given by

$$P_i = F(Z) = 1/(1+e^{-Z})$$

where F () is the logistic cumulative distribution function, and Z is the linear combination

$$Z = \beta_0 + \beta_1 \text{AGE} + \beta_2 \text{HSTINF} + \beta_3 \text{MSM} + \beta_4 \text{MSS} + \beta_5 \text{MSLWP} + \beta_6 \text{EDUUN} + \beta_7 \text{EDUOA} + \beta_8 \text{EDUNO} + \beta_9 \text{RACEW} + \beta_{10} \text{RACEB} + \beta_{11} \text{RACEO} + \beta_{12} \text{EM} + \beta_{13} \text{AGE1SI} + \beta_{14} \text{CPILL} + \beta_{15} \text{CCON} + \beta_{16} \text{CCAP} + \beta_{17} \text{CFE} + \beta_{18} \text{CIUCD} + \beta_{19} \text{CO} + \beta_{20} \text{CNONE} + \beta_{21} \text{CCONT} + \beta_{22} \text{CCONECON} + \beta_{23} \text{MENL3M} + \beta_{24} \text{MENNL3M} + \beta_{25} \text{MENLY} + \beta_{26} \text{MENL5Y} + \beta_{26} \text{SVD} + \beta_{27} \text{SPPU} + \beta_{28} \text{SPUMOTN} + \beta_{29} \text{SPLA} + \beta_{30} \text{SBBP}$$

where,

AGE	Patient age (in 1997)
HSTINF	previous history of sexually transmitted infection
MSM	marital status, married
MSS	Marital status, single
MSLWP	Marital status, living with partner
EDUUN	Education, degree level
EDUOA	Education, 'A' level/Scottish Higher
EDUNO	Education, 'O' level/CSE/GCSE
RACEW	Ethnicity, white
RACEB	Ethnicity, black
RACEO	Ethnicity, other
EM	Employment status,
AGE1SI	Age at 1st sexual intercourse
CPILL	Contraceptives, pill
CCON	Contraceptives, condom
CCAP	Contraceptives, cap
CFE	Contraceptives, femidom
CIUCD	Contraceptives, IUCD
CO	Contraceptives, withdrawal
CNONE	Contraceptives, none
CCONT	Contraceptives, combination
CCONECON	Contraceptives, combination (exc. condom)
MENL3M	No. of men in last 3 months for sexual intercourse
MENNL3M	No. of new men in last 3 months for sexual intercourse
MENLY	No. of men in previous year for sexual intercourse
MENL5Y	No. of men in last 5years for sexual intercourse
SVD	Vaginal discharge
SPPU	Symptoms - pain passing urine
SPUMOTN	Symptoms - passing urine more often
SPLA	Symptoms - pain lower abdomen
SBBP	Symptoms - bleeding bet periods
SBAS	Symptoms - bleeding after sex
SPDS	Symptoms - pain during sex
SNONE	Symptoms – none

PPULADS	Composite symptoms - pain passing urine, lower abdomen or during sex
BBPOAS	Composite symptoms - periods or sex
CSYMP	Composite symptoms
PWHOP	Partner who has other sexual partners
PWHCGS	Partner with genital symptoms

Thus, Z is a linear function of the explanatory variables describing the patients characteristics such as age and behaviour, where e is the base of the natural logarithms and P_I is the probability that a patient is infected, given the variables in Z. Finally, the addition of an error term, the co-efficient (β_s) can be estimated by the Maximum Likelihood Method.

7-3 Results

A total of 388 patient records were evaluable, of these 8% tested positive for *Chlamydia* trachomatis. Table 7.1 summarises the demographic characteristics of women who tested positive (group 1) and for women who tested negative (group 2).

Table 7.1: Demographic characteristics of patients

	Positive (group 1)	(%)	Negative (group 2)	%
	N = 31	8	N= 357	92
Age (yrs)				
≤19	11	35.5	45	12.6
20-24	10	32.2	89	24.9
25-29	9	29.1	110	30.8
30-34			65	18.3
35-39	1	3.2	23	6.4
40-44			16	4.5
≥ 45			9	2.5
Marital status				
married	1	3.2	42	11.8
single	22	71.0	220	61.6
living with partner	8	25.8	95	26.6
Ethnic race				
White	17	54.8	245	68.6
Black	13	41.9	76	21.3
Other	1	3.2	34	9.5
Education				
University	7	22.6	136	38.1
A level/Scottish highers	21	67.7	184	51.5
CSE/O level/GCSE	3	9.7	34	9.5
Employment status				
Employed	21	67.7	269	75.4
Unemployed	10	32.3	88	24.6

A marked difference across some of the age groups was observed between the two groups of patients. In group 1, women aged 19 or less accounted for 36% compared to a much lower figure of 13% in group 2. Similarly, for the age group 20-24, a higher proportion of women was represented in group 1, 32% compared to 25% in group 2. The marital status of women also differed between groups 1 and 2. In group 1, only 3% of women were married, 25% were living with a partner and the vast majority of 71% were single compared to 12%, 27% and 62% respectively in group 2. A difference in the range of ethnic minorities was observed across both groups. In group, 55% of women were white, 42% black

and 3% were identified as other, compared to 69%, 21% and 10% respectively in group 2. The socio-economic status of women also differed across both groups. Approximately 22% of women in group 1 were educated to university level compared to 38% in group 2. Similarly, a lower proportion of women in group 1 was in employment, 68% compared to 75% in group 2.

The behavioural characteristics of patients are illustrated in table 7.2. The vast majority of women had their first sexual intercourse at the age of 16 yrs in both groups 1 and 2, 39% and 20% respectively. In terms of the type of contraceptive methods used, there was little difference between the two groups, with the exception of higher use of pills in group 1, 71% vs 52%, higher use of femidom, 3 % vs 1%, higher use of a combination of contraceptives, 100% vs 92%. There was little difference in terms of the number of sexual partners for both groups of patients.

Table 7.2 Behavioural characteristics of patients

	Positive (group 1)	(%)	Negative (group 2)	%
	N = 31	8	N= 357	92
Age at first sexual intercourse				
Modal age for both groups = 16 yrs	12	38.7	70	19.8
Contraceptive methods				
Pill	22	71.0	187	52.4
Condom	24	77.4	264	73.9
Cap	1	3.2	11	3.1
Femidom	1	3.2	3	0.8
Coil/IUCD	3	9.7	27	7.6
Withdrawal	1	3.2	36	10.1
Combination	31	100	329	92.2
Combination (exc condom)	25	80.6	239	66.9
None	0	0	47	13.2
Number of sexual partners				
last 3 months (1/2/3/>3)	21/9/0/1		267/42/13/5	
last 12 months (1/2/3/>3)	14/8/3/6		179/77/27/51	
last 5 yrs (1/2/3/>3)	4/4/3/14		75/61/45/135	
Number of new sexual partners				
last 3 months	11/2/1		81/18/6/3	

Table 7.3 below illustrates the clinical characteristics for patients in groups 1 and 2. A small difference was observed between the groups in terms of a history of sexually transmitted diseases, 23% in group 1 compared to 27% in group 2. In terms of signs and symptoms present, there appears to be a small variation amongst some of the symptoms, primarily vaginal discharge (52% vs 42%), pain in lower abdomen (19% vs 30%), bleeding between periods (3% vs 13%), pain during sex (10% vs 26%) and a partner who has complained of genital symptoms (32% vs 20%).

Table 7.3 Clinical characteristics of patients

	Positive (group 1)	(%)	Negative (group 2)	%
	N = 31	8	N= 357	92
History of STD	7	22.6	96	26.9
Signs & symptoms present				
Vaginal discharge	16	51.6	148	41.5
Pain passing urine	6	19.4	62	17.4
Pain passing urine more often	6	19.4	55	15.4
Pain, lower abdomen	6	19.4	106	29.7
Bleeding between periods	1	3.2	47	13.2
Bleeding after sex	2	6.5	22	6.2
Pain during sex	3	9.7	91	25.5
No symptoms	8	25.8	97	27.2
Pain passing urine, lower abdomen or during sex	11	35.5	171	47.9
Bleeding between periods or after sex	3	9.7	61	17.1
Composite symptoms	23	74.2	262	73.4
Partner who has other sexual partners	5	16.1	52	14.6
Partner with genital symptoms	10	32.3	72	20.2

The table below illustrates the results of the regression analysis conducted to determine risk factors associated with *Chlamydia* infection.

Table 7.4 Correlates of *Chlamydia* infection by regression analysis in a sample of women presenting in a GUM in England

	B	S.E.	Wald	Sig.	Exp(B)
AGE	-.125	.037	11.251	.001	.882
AGE1SI	-.285	.156	3.329	.068	.752
SVD	2.013	.971	4.297	.038	7.487
PWHCGS	1.371	.666	4.237	.040	3.938

The significant variables include age, signs and symptoms (vaginal discharge and pain passing urine) and partner who complains of genital symptoms. Age at first sexual intercourse was almost statistically significant at the 95% level (0.06), however all other variables including the number of sexual partners were not found to be associated with *Chlamydia* infection.

7-4 Discussion

In general, the results of this study confirm results obtained in other countries. The prevalence rate of 8% represents an average across different health care settings, although it is lower than expected for a specialist GUM clinic. Women with less education, less likely to be married and who are black appear to be at higher risk of infection. However, the results of this study differ in relation to the number and frequency of partners. The results of this study are dependent on the reliability of the data and in particular how truthfully the questions are answered for an infection, which is socially stigmatised.

The issue of when and who to screen for infection is problematic as the majority of infected women have mild symptoms or none at all. The findings of this study demonstrate demographic, behavioural and clinical characteristics can identify women at high risk for *Chlamydia* infection. Whilst this data has been collected from a specialist clinic, the benefits of using these criteria in primary care are likely to be significant. *Facilitating the use of criteria to help clinicians select patients for screening can control chlamydia infections.* A strategy for selective screening for *Chlamydia* infections based upon risk factors provides an alternative to screening all sexually active women presenting to GUM clinics. This is particularly important if the prevalence of infection is low. Finally, the consequences of false-positive tests are reduced when more selective screening criteria are used.

CHAPTER EIGHT

CONCLUSIONS

Making decisions in health care is complex and is often based on clinical experience and intuition. Decision analysis is an important tool in the evaluation of health care. This method allows the individual decision-maker to construct a logical and rational model of the decision problem. Probability estimates and costs of alternative management strategies are incorporated to provide the most cost-effective option. Decision analysis is now beginning to play a more prominent role in health economic as evaluators recognise the advantages of this method of solving problems. Nevertheless, there remain a number of methodological and practical shortcomings. However, with continued efforts in research it is predicted that the science of Decision Analysis will be advanced. Although methodological improvements can be made, it is far more difficult to change the approach of individual decision-makers. If, as the critics claim, the individual is a basically irrational decision-maker then improvements in the methodology are unlikely to affect the decision process. It is therefore proposed that alongside continued research efforts, a programme of educating decision-makers on the merits and methods of performing decision analysis are equally, if not more important.

This thesis has focused on the term 'rational prescribing'. It has been shown that the interpretation of this widely used term depends very much on the perspective of the user. Thus, a clinician's view of rational may not necessarily

coincide with that of an economist, nor the government. Initiatives to promote rational prescribing have been in existence for some time. However, attempting to define *rational* prescribing is a difficult task. The interpretation depends very much on the context within which it is used. Thus, for an economist, *rational* is synonymous with *Homo Economicus* where consumers (the decision-makers) maximise their utility given cost constraints. Trade-offs between different types of goods are made using a utility function. In medicine, it is often easier to define irrational prescribing. Nevertheless, a rational diagnosis of a patient entails diagnosing a disease using published assessments on the probability of the disease.

Policy-makers interpretation of rational prescribing and to a large extent rational decision making, appears to be synonymous with the term cost-containment. Drug costs in particular, have been targeted by government policies as a method of containing the overall costs of healthcare. The government has attempted to control the costs of drugs and the quantity of drugs prescribed through various measures aimed at curbing demand. The most consistent policy has been the use of prescription charges. The real charge for prescriptions has increased by 80% over the ten-year period between 1983 and 1993. These charges represent approximately 44% of the Net Ingredient Costs of drugs. However, the increase in costs of drugs has been lower than the increase in prescription charges. The effect of such a policy has been a reduction in the average number of prescription items received by patients eligible for prescription charges. However, this effect may be ameliorated by the tendency of some doctors to prescribe larger quantities of drugs per item. In the case of antibiotics however, this is unlikely to be the case, as these drugs are not usually prescribed

in large quantities, as there would not be any clinical benefits in doing so. Nevertheless, the success of a policy of prescription charges is constrained by the number of people who are eligible for exemptions to prescription charges. In addition, high consumers of drugs often purchase exemption certificates thereby waiving prescription charges for a small fee. Only 15% of prescriptions are actually paid for, therefore drastically limiting the potential for reducing costs of treatment and unnecessary prescribing. A selected list has been in place since 1995. The purpose of this list is to limit the type of drugs doctors are allowed to prescribe. In general, more of the expensive brand drugs may not be prescribed on the NHS. Although, there was a one-off savings in drug expenditures it does not seem to have halted the increase in drug expenditure. A third policy has been the education of doctors. Information and advice on prescribing rationally is sent out to GPs in the form of bulletins (BNF, Drug and Therapeutics bulletin, ABPI data sheet compendium etc.) More importantly, the Prescription Pricing Authority provides individual PACT data to each doctor on a quarterly basis. Additional details of prescribing are sent to those doctors who are expensive prescribers. Any doctor requiring more detailed information on his/her prescribing patterns can also request such information. The effects of such a policy are difficult to assess; however, it can be assumed that education of prescribers should lead to more appropriate use of treatments. However, this may not necessarily coincide with attempts to reduce costs of the drug bill. Indicative prescribing amounts are set by FHSAs in consultation with doctors. Monthly reports are then sent to each practice by the PPA to show levels of expenditure in relation to the initial budget set. Again there is little evidence to show if this policy has helped to contain costs of drugs.

Chlamydia represents a significant economic burden despite the availability of effective antibiotic treatments. This thesis has demonstrated the extent of the economic burden of *Chlamydia* in England, Wales and Scotland at approximately £108 million annually. The direct costs, £65m account for 60% of the total costs.

A prevalence rate of 8% was found amongst a population of women presenting to a GUM clinic. The risk factors associated with *Chlamydia* infection have been identified as patient age, some clinical signs, age at first sexual intercourse and a partner who complains of genital symptoms. In general, these results confirm the finding of similar studies conducted in the U.S. The question of whom to screen for tests is problematic. The results of this research illustrate behavioural, clinical and demographic variables may be used to identify patients who should be screened. Thus, a strategy for selective screening for *Chlamydia* infections based upon risk factors provides an alternative to screening all sexually active women. This is particularly important if the prevalence rate is low. A number of antibiotic treatments are available for the management of *Chlamydia*. The application of decision analysis clearly demonstrates treatment with a single dose of azithromycin is a cost-effective treatment strategy.

In terms of recommendations, this research suggests asymptomatic individuals should be screened only if a number of risk factors have been identified. Upon confirmation of tests, treatment with azithromycin should be initiated. The appropriate management of infections caused by *Chlamydia* trachomatis will lead to a more efficient allocation of resources within healthcare.

There is increased awareness of the need for collecting and analysing information based on proven scientific evidence of efficacy for choice of treatments in health care. The role of government policies is to encourage

whenever possible, the use of low cost drugs, despite the fact that such treatments represent a small fraction of the overall costs of healthcare. Health economics provides policy makers with evidence of the cost-effectiveness, or lack of, for current therapeutic options. However, a focus on simply one aspect of the management of a disease can be extremely misleading. Thus, regulations or guidelines should review the economic evidence and then provide guidance on the management of the whole disease area.

Although, an increasing number of clinical decision analyses are being carried out, similar rates of published studies incorporating economic data are lacking. This thesis adds to the existing body of research in this important public health issue however it represents just the start of the research that is required to make rational decisions. The thesis has contributed to research in three main areas (1) evaluate the current economic burden associated with Chlamydia in the UK, (2) identify risk factors associated with *Chlamydia* infection, and (3) determine cost effective treatment options for diagnosed patients.

Suggestions for further research include (1) conducting similar studies on a national basis in order to assess the generalisability of results obtained from one GUM clinic in London (2) prospective collection of resource utilisation data in order to assess the real world clinical and cost-effectiveness of identifying individuals at risk for *Chlamydia,* and (3) evaluate cost-effectiveness of treatment for patients with a presumptive diagnosis of *Chlamydia*.

APPENDIX A

Cost of illness study definitions

Definitions for Chlamydia

International Classification Diseases, 9th revision (first 3 digits only) in MSGP4

Uncomplicated chlamydia

0	Other diseases due to viruses and chlamydiae
0	Complicated chlamydia

Complicated chlamydia

598	Urethral stricture
599	Other disorders of the urethra and urinary tract
601	Inflammatory disease of prostate
604	Orchitis & epididymitis
606	Infertility, male
615	Inflammatory disease uterus, except cervix
616	Inflammatory disease cervix, vagina & vulva
617	Infertility, female
633	Ectopic pregnancy

International Classification Diseases, 9th revision (first 3 digits only) in HES

Diagnostic short codes (GUM clinic data)

Uncomplicated Chlamydia

C4A, C4C	Uncomplicated chlamydia infection
C4E	Epidemiological treatment of suspected chlamydia
C4H	Uncomplicated non-gonococcal/non-specific urethritis*
C41	Epidemiological treatment of NSGI*

Complicated chlamydia

C4B	Complicated chlamydia infection
C4D	Chlamydia ophthalmia neonatorum*
	Assume 1% due to complicated chlalydia

Mortality statistics

614-616	Inflammtory disease of female pelvic organs

APPENDIX B

Questionnaire used to collect information on patients presenting in GUM clinics

1. What was your age on your last birthday?

-------- yrs

2. Are you: (please tick box)

Married ☐1
Living with a Partner ☐2
Widowed/Divorced/Separated ☐3
Single ☐4

3. Have you passed any of the following exams? (Please tick)

CSE/'O' Level/GCSE ☐1
A' Level/Scottish Highers/or equivalent ☐2
Degree (University or Polytechnic) ☐3
None ☐4

4. To which of these groups do you consider you belong? (Please tick)

White ☐10 Indian ☐50 Asian, other ☐90
Black Caribbean ☐20 Chinese ☐60 Other ethnic group ☐95
Black African ☐30 Bangladeshi ☐70
Black, other ☐40 Pakistani ☐80

5. Are you currently

Employed ☐1
Unemployed ☐2

6. Have you had sexual intercourse with a man?

Yes ☐

No ☐ ⇒ Thank you for filling in the questionnaire so far. You do not need to continue. Please put this in the envelope provided and give it to the doctor or nurse when you see them.

7. How old were you when you first had sexual intercourse with a man?

Age .....yrs

8. Which of the following birth control methods have you used <u>at all</u> with a partner in the last year? (tick as many boxes as you need)

The Pill	☐11
Condom/Sheath /Durex	☐12
Cap/Diaphragm	☐13
Femidom	☐14
IUCD (Coil)	☐15
Withdrawal	☐16
None	☐17
Others (Please specify)	☐99 .....

9. With how many men have you had sexual intercourse?

In the last 3 months (whether just once, a few times, a regular partner or husband)?

.....

How many of these were new partners with whom you had not had sex before?

.....

10. With how many men have you had sexual intercourse:

in the last year (whether a regular partner or husband, once or a few times)?

.....

in the last 5 years (whether a regular partner or husband, once or a few times)?

.....

11. Have you ever had a sexually transmitted infection?

Yes ☐1

No ☐0

12. Do you have any of the following problems at the moment? (Tick as many as you need)

Vaginal discharge that is not normal for you	☐11
Pain when you pass urine	☐12
Passing urine more often than is normal for you	☐13
Pain in your lower abdomen other than during periods	☐14
Bleeding between periods	☐15
Bleeding after sex	☐16
Pain during sex	☐17
None	☐99

13. Do you have a partner who has other partners as well as you?

Yes ☐1
No ☐0

14. Do you have a partner who has complained of genital symptoms?

Yes ☐1
No ☐0

15. Had you heard of Chlamydia before today?

Yes ☐1
No ☐0

IF YOU ARE WORRIED ABOUT ANY OF THESE PROBLEMS PLEASE TALK TO THE NURSE. THIS QUESTIONNAIRE WILL NOT BE SEEN BY ANYONE IN THE CLINIC. THANK YOU VERY MUCH FOR COMPLETING THIS QUESTIONNAIRE. PLEASE PUT IT IN THE ENVELOPE PROVIDED AND GIVE IT TO THE DOCTOR OR NURSE WHEN YOU SEE THEM.

Office Use Only

☐
☐

APPENDIX C

Statistical reports for chapter seven

PATIENT	Patient identification number
CHLA	Chlamydia status
AGE	Patient age (in 1997)
MSM	Marital status, married
MSS	Marital status, single
MSLWP	Marital status, living with partner
EDUUN	Education, degree level
EDUOA	Education, 'A' level/Scottish Higher
EDUNO	Education, 'O' level/CSE/GCSE
RACEW	Ethnicity, white
RACEB	Ethnicity, black
RACEO	Ethnicity, other
EM	Employment status,
AGE1SI	Age at 1st sexual intercourse
CPILL	Contraceptives, pill
CCON	Contraceptives, condom
CCAP	Contraceptives, cap
CFE	Contraceptives, femidom
CIUCD	Contraceptives, IUCD
CO	Contraceptives, withdrawal
CNONE	Contraceptives, none
CCONT	Contraceptives, combination
CCONECON	Contraceptives, combination (exc condom)
MENL3M	No. of men in last 3 months for sexual intercourse
MENNL3M	No. of new men in last 3 months for sexual intercourse
MENLY	No. of men in previous year for sexual intercourse
MENL5Y	No. of men in last 5years for sexual intercourse
HSTINF	History of sexually transmitted infection
SVD	Vaginal discharge
SPPU	Symptoms - pain passing urine
SPUMOTN	Symptoms - passing urine more often
SPLA	Symptoms - pain lower abdomen
SBBP	Symptoms - bleeding bet periods
SBAS	Symptoms - bleeding after sex
SPDS	Symptoms - pain during sex
SNONE	Symptoms – none
PPULADS	Composite symptoms - pain passing urine, lower abdomen or during sex
BBPOAS	Composite symptoms - bleeding between periods or after sex
CSYMP	Composite symptoms
PWHOP	Partner who has other sexual partners
PWHCGS	Partner with genital symptoms

Frequencies

AGE1SI

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	9	1	.3	.3	.3
		12	5	1.4	1.4	1.7
		13	7	2.0	2.0	3.7
		14	16	4.5	4.5	8.2
		15	47	13.2	13.3	21.5
		16	2	.6	.6	22.1
		16	68	19.0	19.3	41.4
		17	1	.3	.3	41.6
		17	55	15.4	15.6	57.2
		18	51	14.3	14.4	71.7
		19	2	.6	.6	72.2
		19	36	10.1	10.2	82.4
		20	16	4.5	4.5	87.0
		21	19	5.3	5.4	92.4
		22	8	2.2	2.3	94.6
		23	8	2.2	2.3	96.9
		25	5	1.4	1.4	98.3
		26	2	.6	.6	98.9
		27	1	.3	.3	99.2
		28	1	.3	.3	99.4
		29	1	.3	.3	99.7
		30	1	.3	.3	100.0
		Total	353	98.9	100.0	
	Missing	System	4	1.1		
	Total		357	100.0		
1	Valid	14	4	12.9	13.3	13.3
		15	4	12.9	13.3	26.7
		16	1	3.2	3.3	30.0
		16	12	38.7	40.0	70.0
		17	1	3.2	3.3	73.3
		17	1	3.2	3.3	76.7
		17	4	12.9	13.3	90.0
		18	2	6.5	6.7	96.7
		19	1	3.2	3.3	100.0
		Total	30	96.8	100.0	
	Missing	System	1	3.2		
	Total		31	100.0		

		28	2	6.5	6.5	93.5

CFE

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	354	99.2	99.2	99.2
		1	3	.8	.8	100.0
		Total	357	100.0	100.0	
1	Valid	0	30	96.8	96.8	96.8
		1	1	3.2	3.2	100.0
		Total	31	100.0	100.0	

CIUCD

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	330	92.4	92.4	92.4
		1	27	7.6	7.6	100.0
		Total	357	100.0	100.0	
1	Valid	0	28	90.3	90.3	90.3
		1	3	9.7	9.7	100.0
		Total	31	100.0	100.0	

CPILL

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	170	47.6	47.6	47.6
		1	187	52.4	52.4	100.0
		Total	357	100.0	100.0	
1	Valid	0	9	29.0	29.0	29.0
		1	22	71.0	71.0	100.0
		Total	31	100.0	100.0	

CO

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	321	89.9	89.9	89.9
		1	36	10.1	10.1	100.0
		Total	357	100.0	100.0	
1	Valid	0	30	96.8	96.8	96.8
		1	1	3.2	3.2	100.0
		Total	31	100.0	100.0	

CCON

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	93	26.1	26.1	26.1
		1	264	73.9	73.9	100.0
		Total	357	100.0	100.0	
1	Valid	0	7	22.6	22.6	22.6
		1	24	77.4	77.4	100.0
		Total	31	100.0	100.0	

CCONT

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	28	7.8	7.8	7.8
		1	329	92.2	92.2	100.0
		Total	357	100.0	100.0	
1	Valid	1	31	100.0	100.0	100.0

CCAP

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	346	96.9	96.9	96.9
		1	11	3.1	3.1	100.0
		Total	357	100.0	100.0	
1	Valid	0	30	96.8	96.8	96.8
		1	1	3.2	3.2	100.0
		Total	31	100.0	100.0	

MENL3M

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	23	6.4	6.6	6.6
		1	267	74.8	76.3	82.9
		2	42	11.8	12.0	94.9
		3	13	3.6	3.7	98.6
		4	1	.3	.3	98.9
		5	1	.3	.3	99.1
		7	1	.3	.3	99.4
		30	1	.3	.3	99.7
		200	1	.3	.3	100.0
		Total	350	98.0	100.0	
	Missing	System	7	2.0		
	Total		357	100.0		
1	Valid	1	21	67.7	67.7	67.7
		2	9	29.0	29.0	96.8
		5	1	3.2	3.2	100.0
		Total	31	100.0	100.0	

CCONECON

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	118	33.1	33.1	33.1
		1	239	66.9	66.9	100.0
		Total	357	100.0	100.0	
1	Valid	0	6	19.4	19.4	19.4
		1	25	80.6	80.6	100.0
		Total	31	100.0	100.0	

MENL5Y

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	3	.8	.9	.9
		1	75	21.0	23.7	24.7
		2	61	17.1	19.3	44.0
		3	45	12.6	14.2	58.2
		4	32	9.0	10.1	68.4
		5	18	5.0	5.7	74.1
		6	18	5.0	5.7	79.7
		7	12	3.4	3.8	83.5
		8	10	2.8	3.2	86.7
		9	2	.6	.6	87.3
		10	14	3.9	4.4	91.8
		11	2	.6	.6	92.4
		13	5	1.4	1.6	94.0
		14	2	.6	.6	94.6
		15	7	2.0	2.2	96.8
		16	1	.3	.3	97.2
		17	1	.3	.3	97.5
		18	2	.6	.6	98.1
		20	3	.8	.9	99.1
		25	1	.3	.3	99.4
		30	1	.3	.3	99.7
		40	1	.3	.3	100.0
		Total	316	88.5	100.0	
	Missing	System	41	11.5		
	Total		357	100.0		
1	Valid	1	4	12.9	16.0	16.0
		2	4	12.9	16.0	32.0
		3	3	9.7	12.0	44.0
		4	3	9.7	12.0	56.0
		6	1	3.2	4.0	60.0
		7	2	6.5	8.0	68.0
		8	4	12.9	16.0	84.0
		9	1	3.2	4.0	88.0
		10	1	3.2	4.0	92.0
		15	1	3.2	4.0	96.0
		17	1	3.2	4.0	100.0
		Total	25	80.6	100.0	
	Missing	System	6	19.4		
	Total		31	100.0		

SVD

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	209	58.5	58.5	58.5
		1	148	41.5	41.5	100.0
		Total	357	100.0	100.0	
1	Valid	0	15	48.4	48.4	48.4
		1	16	51.6	51.6	100.0
		Total	31	100.0	100.0	

SPPU

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	295	82.6	82.6	82.6
		1	62	17.4	17.4	100.0
		Total	357	100.0	100.0	
1	Valid	0	25	80.6	80.6	80.6
		1	6	19.4	19.4	100.0
		Total	31	100.0	100.0	

HSTINF

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	260	72.8	73.0	73.0
		1	96	26.9	27.0	100.0
		Total	356	99.7	100.0	
	Missing	System	1	.3		
	Total		357	100.0		
1	Valid	0	24	77.4	77.4	77.4
		1	7	22.6	22.6	100.0
		Total	31	100.0	100.0	

SPUMOTN

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	302	84.6	84.6	84.6
		1	55	15.4	15.4	100.0
		Total	357	100.0	100.0	
1	Valid	0	25	80.6	80.6	80.6
		1	6	19.4	19.4	100.0
		Total	31	100.0	100.0	

SPLA

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	251	70.3	70.3	70.3
		1	106	29.7	29.7	100.0
		Total	357	100.0	100.0	
1	Valid	0	25	80.6	80.6	80.6
		1	6	19.4	19.4	100.0
		Total	31	100.0	100.0	

SBBP

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	310	86.8	86.8	86.8
		1	47	13.2	13.2	100.0
		Total	357	100.0	100.0	
1	Valid	0	30	96.8	96.8	96.8
		1	1	3.2	3.2	100.0
		Total	31	100.0	100.0	

SBAS

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	335	93.8	93.8	93.8
		1	22	6.2	6.2	100.0
		Total	357	100.0	100.0	
1	Valid	0	29	93.5	93.5	93.5
		1	2	6.5	6.5	100.0
		Total	31	100.0	100.0	

SPDS

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	266	74.5	74.5	74.5
		1	91	25.5	25.5	100.0
		Total	357	100.0	100.0	
1	Valid	0	28	90.3	90.3	90.3
		1	3	9.7	9.7	100.0
		Total	31	100.0	100.0	

PPULADS

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	186	52.1	52.1	52.1
		1	171	47.9	47.9	100.0
		Total	357	100.0	100.0	
1	Valid	0	20	64.5	64.5	64.5
		1	11	35.5	35.5	100.0
		Total	31	100.0	100.0	

BBPOAS

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	296	82.9	82.9	82.9
		1	61	17.1	17.1	100.0
		Total	357	100.0	100.0	
1	Valid	0	28	90.3	90.3	90.3
		1	3	9.7	9.7	100.0
		Total	31	100.0	100.0	

CSYMP

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	95	26.6	26.6	26.6
		1	262	73.4	73.4	100.0
		Total	357	100.0	100.0	
1	Valid	0	8	25.8	25.8	25.8
		1	23	74.2	74.2	100.0
		Total	31	100.0	100.0	

PWHOP

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	295	82.6	85.0	85.0
		1	52	14.6	15.0	100.0
		Total	347	97.2	100.0	
	Missing	System	10	2.8		
	Total		357	100.0		
1	Valid	0	25	80.6	83.3	83.3
		1	5	16.1	16.7	100.0
		Total	30	96.8	100.0	
	Missing	System	1	3.2		
	Total		31	100.0		

PWHCGS

CHLA			Frequency	Percent	Valid Percent	Cumulative Percent
0	Valid	0	281	78.7	79.6	79.6
		1	72	20.2	20.4	100.0
		Total	353	98.9	100.0	
	Missing	System	4	1.1		
	Total		357	100.0		
1	Valid	0	18	58.1	64.3	64.3
		1	10	32.3	35.7	100.0
		Total	28	90.3	100.0	
	Missing	System	3	9.7		
	Total		31	100.0		

Logistic Regression

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	4.954	8	.763

Contingency Table for Hosmer and Lemeshow Test

		CHLA = 0		CHLA = 1		Total
		Observed	Expected	Observed	Expected	
Step 1	1	29	29.000	0	.000	29
	2	29	29.000	0	.000	29
	3	29	28.999	0	.001	29
	4	29	28.925	0	.075	29
	5	29	28.666	0	.334	29
	6	27	28.307	2	.693	29
	7	27	27.605	2	1.395	29
	8	28	26.551	1	2.449	29
	9	26	24.561	3	4.439	29
	10	20	21.384	13	11.616	33

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1	MSM	-6.697	39.423	.029	1	.865	.001
	MSS	.807	.810	.992	1	.319	2.240
	EDUUN	.217	1.412	.024	1	.878	1.242
	EDUOA	.345	1.325	.068	1	.795	1.412
	RACEW	1.651	1.441	1.313	1	.252	5.214
	RACEB	1.768	1.504	1.381	1	.240	5.858
	EM	-.388	.736	.278	1	.598	.678
	AGE1SI	-.285	.156	3.329	1	.068	.752
	CPILL	.412	2.066	.040	1	.842	1.510
	CCON	-.326	.829	.155	1	.694	.722
	CCAP	-7.296	73.129	.010	1	.921	.001
	CFE	1.372	2.120	.419	1	.517	3.945
	CIUCD	-.286	1.915	.022	1	.881	.751
	CO	-8.584	43.636	.039	1	.844	.000
	CNONE	-8.741	58.307	.022	1	.881	.000
	CCONT	1.170	72.426	.000	1	.987	3.223
	CCONECON	-.272	2.187	.015	1	.901	.762
	MENL3M	.007	.136	.002	1	.962	1.007
	MENNL3M	-.081	.502	.026	1	.872	.922
	MENLY	-.031	.226	.018	1	.892	.970
	MENL5Y	.086	.090	.920	1	.337	1.090
	HSTINF	-.827	.736	1.261	1	.262	.438
	SVD	2.013	.971	4.297	1	.038	7.487
	SPPU	1.086	1.323	.674	1	.412	2.964
	SPUMOTN	-.064	.842	.006	1	.939	.938
	SPLA	-.671	1.362	.243	1	.622	.511
	SBBP	-7.410	134.998	.003	1	.956	.001
	SBAS	-5.959	135.001	.002	1	.965	.003
	SPDS	-1.449	1.200	1.459	1	.227	.235
	SNONE	-5.702	177.220	.001	1	.974	.003
	PPULADS	-.103	1.559	.004	1	.947	.902
	BBPOAS	7.155	135.006	.003	1	.958	1280.221
	CSYMP	-6.800	177.223	.001	1	.969	.001

PWHOP	.341	.815	.175	1	.676	1.406
PWHCGS	1.371	.666	4.237	1	.040	3.938
Constant	4.325	191.472	.001	1	.982	75.579

a Variable(s) entered on step 1: MSM, MSS, EDUUN, EDUOA, RACEW, RACEB, EM, AGE1SI, CPILL, CCON, CCAP, CFE, CIUCD, CO, CNONE, CCONT, CCONECON, MENL3M, MENNL3M, MENLY, MENL5Y, HSTINF, SVD, SPPU, SPUMOTN, SPLA, SBBP, SBAS, SPDS, SNONE, PPULADS, BBPOAS, CSYMP, PWHOP, PWHCGS.

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Step number: 1

             Observed Groups and Predicted Probabilities

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⇔
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⇕
E        ⇔0
⇔
Q        ⇔0
⇔
U        ⇔0
⇔
E     80 ⇕0
⇕
N        ⇔0
⇔
C        ⇔0
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Y        ⇔0
⇔
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⇔
         ⇔000  0
⇔
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⇔
Predicted
⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇕⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇕⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇩⇕⇩⇩⇩⇩⇩⇩
⇩⇩⇩⇩⇩⇩⇩⇩⇩
  Prob:   0              .25              .5               .75
1
  Group:
000000000000000000000000000000111111111111111111111111111111

          Predicted Probability is of Membership for 1
          The Cut Value is .50
          Symbols: 0 - 0
                   1 - 1
          Each Symbol Represents 10 Cases.
```

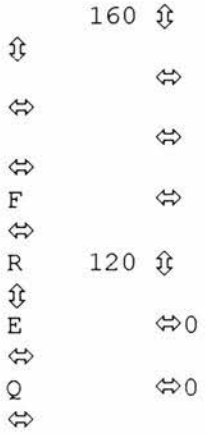
Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1	AGE			11.768	35	1.000	
	AGE(1)	9.510	164.265	.003	1	.954	13489.798
	AGE(2)	8.257	164.264	.003	1	.960	3854.228
	AGE(3)	8.257	164.262	.003	1	.960	3854.228
	AGE(4)	9.392	164.262	.003	1	.954	11990.931
	AGE(5)	8.736	164.262	.003	1	.958	6226.060
	AGE(6)	7.430	164.264	.002	1	.964	1686.225
	AGE(7)	7.600	164.262	.002	1	.963	1998.489
	AGE(8)	8.468	164.262	.003	1	.959	4761.105
	AGE(9)	7.900	164.264	.002	1	.962	2697.960
	AGE(10)	8.357	164.262	.003	1	.959	4259.936
	AGE(11)	6.907	164.264	.002	1	.966	999.244
	AGE(12)	6.984	164.264	.002	1	.966	1079.184
	AGE(13)	8.411	164.262	.003	1	.959	4496.599
	AGE(14)	7.952	164.262	.002	1	.961	2839.957
	AGE(15)	7.495	164.264	.002	1	.964	1798.640
	AGE(16)	.000	169.023	.000	1	1.000	1.000
	AGE(17)	.000	170.461	.000	1	1.000	1.000
	AGE(18)	.000	169.648	.000	1	1.000	1.000
	AGE(19)	.000	174.225	.000	1	1.000	1.000
	AGE(20)	.000	170.968	.000	1	1.000	1.000
	AGE(21)	.000	201.178	.000	1	1.000	1.000
	AGE(22)	.000	183.649	.000	1	1.000	1.000
	AGE(23)	.000	175.602	.000	1	1.000	1.000
	AGE(24)	.000	175.602	.000	1	1.000	1.000
	AGE(25)	9.104	164.265	.003	1	.956	8993.198
	AGE(26)	.000	179.939	.000	1	1.000	1.000
	AGE(27)	.000	189.672	.000	1	1.000	1.000
	AGE(28)	.000	189.672	.000	1	1.000	1.000
	AGE(29)	.000	201.178	.000	1	1.000	1.000
	AGE(30)	.000	189.672	.000	1	1.000	1.000
	AGE(31)	.000	201.178	.000	1	1.000	1.000
	AGE(32)	.000	232.300	.000	1	1.000	1.000
	AGE(33)	.000	232.300	.000	1	1.000	1.000
	AGE(34)	.000	201.178	.000	1	1.000	1.000
	AGE(35)	.000	201.178	.000	1	1.000	1.000
	Constant	-10.203	164.261	.004	1	.950	.000

a Variable(s) entered on step 1: AGE.

Step number: 1

Observed Groups and Predicted Probabilities



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⇔
E     80 ⇳0
⇳
N         ⇔0
⇔
C         ⇔0
⇔
Y         ⇔0 0     1
⇔
      40 ⇳0 0     0
⇳
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⇔
          ⇔0 0000 000 1
⇔
          ⇔0 0000 000 0      0
⇔
Predicted
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⇩⇩⇩⇩⇩⇩⇩⇩⇩
  Prob:   0            .25            .5             .75
1
  Group:
000000000000000000000000000000111111111111111111111111111111

          Predicted Probability is of Membership for 1
          The Cut Value is .50
          Symbols: 0 - 0
                   1 - 1
          Each Symbol Represents 10 Cases.
```

Contingency Table for Hosmer and Lemeshow Test

		CHLA = 0 Observed	CHLA = 0 Expected	CHLA = 1 Observed	CHLA = 1 Expected	Total
Step 1	1	35	35.632	1	.368	36
	2	33	32.195	0	.805	33
	3	45	43.291	0	1.709	45
	4	34	35.106	3	1.894	37
	5	24	26.305	4	1.695	28
	6	25	24.231	1	1.769	26
	7	46	45.975	4	4.025	50
	8	27	27.795	4	3.205	31
	9	43	40.243	3	5.757	46
	10	45	46.226	11	9.774	56

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B) Lower	Upp
Step 1	AGE	-.125	.037	11.251	1	.001	.882	.820	.9
	Constant	.634	.874	.527	1	.468	1.885		

a Variable(s) entered on step 1: AGE.

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Step number: 1
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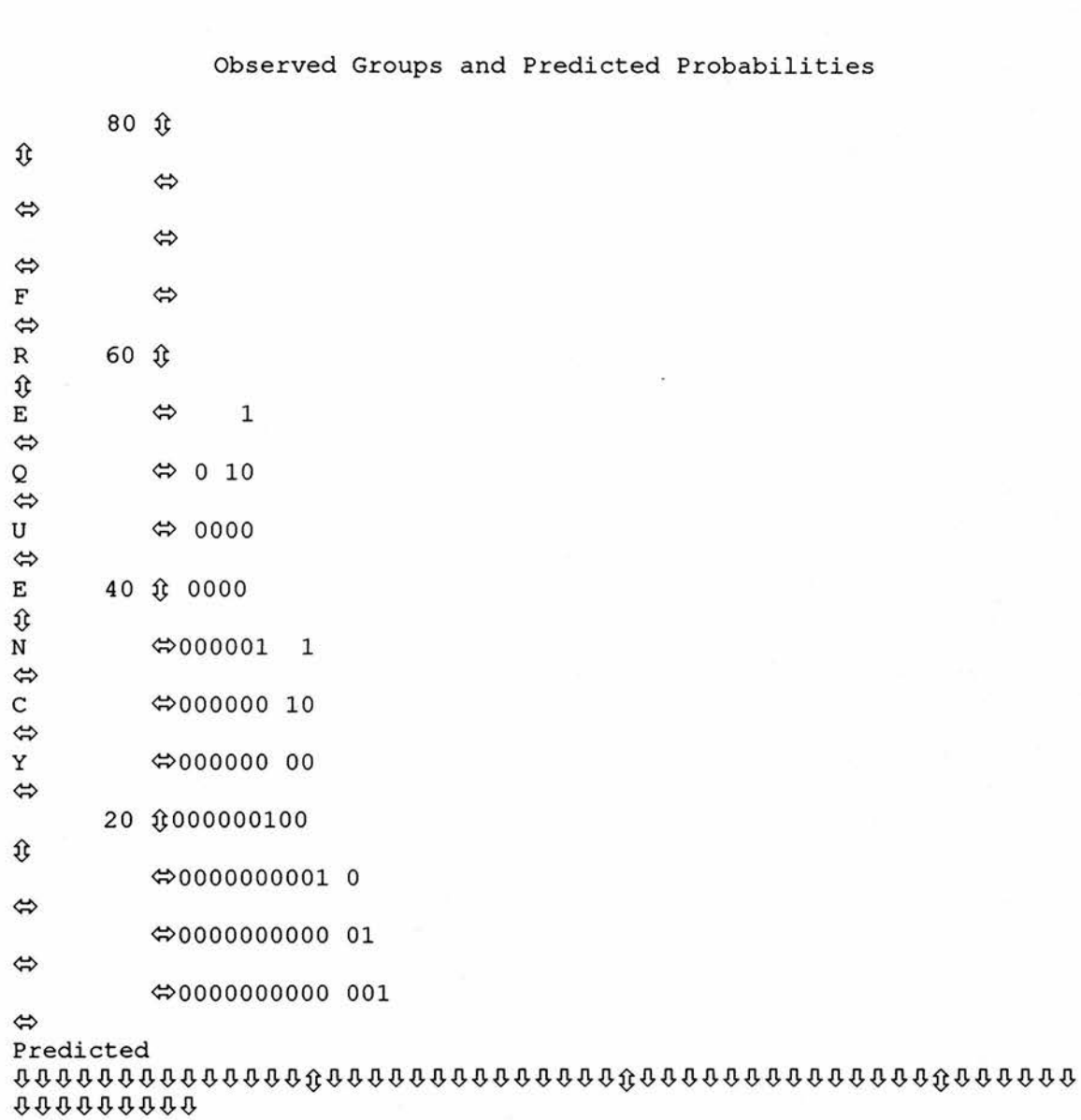
Observed Groups and Predicted Probabilities
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60
40
20
FREQUENCY
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Predicted
Prob: 0 .25 .5 .75 1
Group:
Predicted Probability is of Membership for 1
The Cut Value is .50
Symbols: 0 - 0
1 - 1
Each Symbol Represents 5 Cases.

APPENDIX D

Additional calculations for economic models

Chapter 5

Estimation of number of cases of chlamydia reported to GUM clinics, 1997

Number of cases of chlamydia reported to GUM clinics		Males	Females	% due to chlamydia	Total
Uncomplicated chlamydia					
C4A, C4C	Uncomplicated chlamydia infection	16105	22527	100	38632
C4E	Treatment of suspected chlamydia	7919	6183	100	14102
	Total number of uncomplicated cases	24024	28710		52734
Complicated chlamydia					
C4B	Complicated chlamydia infection	335	1275	100	1610
C4D	Chlamydia ophthalmia neonatorum (infants)	18	13	100	31
C4H	Uncomplicated non-gonococcal/non-specific urethritis	48359	N/A	50	24180
C41	Epidemiological treatment of NSGI	4881	16624	50	10753
C5	Complicated non-gonococcal/non-specific infection	2504	8955	50	5730
	Total number of complicated cases	28225	14078		42303
All cases of Chlamydia		52249	42788		95037

Source: Hughes et. al. 1998

Estimation of productivity loss as a result of managing Chlamydia in GUM clinics

Number of persons	**Male**	**Female**	**Total**
Uncomplicated	24024	28710	52734
Complicated	28225	14078	42303
Total	52249	42788	95237
Number of persons in employment			
Uncomplicated chlamydia			
Full-time	14414	11771	26185
Part-time	721	4881	5602
Complicated chlamydia			
Full-time	16935	4826	21761
Part-time	847	2393	3240
Number of days			
Uncomplicated	14775	14211	28986
Complicated	52075	18068	70143
Total days	66850	32280	99130

Assumptions

The total lost productivity was calculated using the following assumptions

Uncomplicated	1 day lost for full time employees (1 outpatient attendance) 1/2 day lost for part-time employees
Complicated	3 days lost for f/t employees (2 outpatient + 1 inpatient attendance) 1 1/2 days lost for p/t employees

It is assumed that national rates of employment, obtained from Census data (1991) apply to the study population, thus the rates shown below were applied to the total number of persons managed in GUM clinics.

Rates of employment

	Male	Female
F/t	60	41
P/T	3	17

Having obtained the proportion of patients in employment, by gender and type of employment, daily earnings were applied in order to calculate lost productivity. The earnings used are shown below:

Average daily earnings, by gender (New Earnings Survey, 1998)

Male	
F/t employees = 1 day	81.74
P/t employee = 1/2 day	40.87
Female	
F/t employees = 1 day	59.44
P/t employee = 1/2 day	29.72

Cases of Complicated Chlamydia managed in secondary care, hospital sector

		ordinary admissions & day cases combined by diagnoses			
		0-4	15-19	20-44	All ages
233	Conjunctivitis	594	n/a	n/a	921
371	Salpingitis & oophoritis	n/a	117	1838	2341
372	Inflamm dis pelvic...	n/a	1480	14282	17229
376	Infertility, female	n/a	130	26167	26420

		% ordinary admissions & day cases combined by diagnoses			
		0-4	15-19	20-44	% of all ages
233	Conjunctivitis	64.50	n/a	n/a	64.50
371	Salpingitis & oophoritis	n/a	5.00	78.51	84
372	Inflamm dis pelvic...	n/a	8.59	82.90	91
376	Infertility, female	n/a	0.49	99.04	99.53

All age groups		OA	DC	Total	MD	% OA	% DC
233	Conjunctivitis	705	217	922	9.1	76.5	23.5
371	Salpingitis & oophoritis	2028	330	2358	5.1	86.0	14.0
372	Inflamm dis pelvic...	13503	3924	17427	3.1	77.5	22.5
376	Infertility, female	7598	18992	26590	1.5	28.6	71.4

Total number of cases due to persons aged 15-44 + infants.

233	Conjunctivitis	595
371	Salpingitis & oophoritis	1969
372	Inflamm dis pelvic...	15943
376	Infertility, female	26466

Calculation of ordinary admissions and day cases

		OA	DC	Total
233	Conjunctivitis	455	140	595
371	Salpingitis & oophoritis	1694	276	1969
372	Inflamm dis pelvic...	12353	3590	15943
376	Infertility, female	7563	18904	26466

Calculation of OA and DC attributed to Chlamydia

		%			
233	Conjunctivitis	1	5	1	6
371	Salpingitis & oophoritis	50	847	138	985
372	Inflamm dis pelvic...	50	6177	1795	7972
376	Infertility, female	1	76	189	265
Total			7104	2123	9227

Source: Hospital Episodes Statistics, 1996

Estimation of lost productivity for cases of complicated chlamydia managed in general hospitals

	Ordinary admissions (OA)	Mean duration (days)	Day cases (DC)
Salpingitis & oophoritis	847	5.1	138
Inflamm dis pelvic...	6177	3.1	1795
Infertility, female	76	1.5	9452
All cases (number of females)		18485	
		OA	DC
Salpingitis & oophoritis		8555	138
Inflamm dis pelvic...		50034	1795
Infertility, female		494	9452
Lost productivity days		**59082**	**11385**

	Number of persons in employment		***Lost productivity (No. days)***	
Ordinary admissions	*Full time*	*Part-time*	*Full time*	*Part-time*
Salpingitis & oophoritis	347	144	3507	727
Inflamm dis pelvic...	2533	1050	20514	4253
Infertility, female	31	13	203	42
			24224	5022
Day cases				
Salpingitis & oophoritis	57	23	57	12
Inflamm dis pelvic...	736	305	736	153
Infertility, female	3875	1607	3875	803
			4668	968
Total number of productivity days lost				*34881*
Total cost of productivity days lost (£)				**2,073,348**

	Age group			Consultations in scotland, 1997					
	16-24	25-44	Total	15-24	25-44	% due C.T	Total (C.T)	15-24	25-44
Male									
Uncomplicated chlamydia									
Oth diseases due viruses and chlamydiae (070-079)	319	170	281	10623	13226				
077 Oth dis of conjunctiva due to viruses & chlamydiae	0	0			0	100	0		
078 Oth dis. Due to viruses and chlamyiae	242	123	195	8059	9569	100	17628	8059	9569
							17628	8059	9569
Complicated chlamydia									
597 Urethritis, not std, & urethral syndrome	1	3	3	33	233	50	133	17	117
598 Urethral stricture	0	1	3	0	78	50	39	0	39
599 Other disorders of urethra & urinary tract	49	69	125	1632	5368	50	3500	816	2684
604 orchitis & epididymitis	26	49	30	866	3812	30	1403	260	1144
606 Infertility, male	2	16	6	67	1245	1	13	1	12
							5089	1093	3996
Total male consultations							**22717**	**9152**	**13565**
Female									
Uncomplicated chlamydia									0
Oth diseases due viruses and chlamydiae (070-079)	460	234	314	14628	18182			14628	18182
077 Oth dis of conjunctiva due to viruses & chlamydiae	0	0		0	0	100	0	0	0
078 Oth dis. Due to viruses and chlamydiae	323	159	214	10271	12354	100	22626	10271	12354
							22626	10271	12354
Complicated chlamydia									
Inflammatory disease of female pelvic organs (614-616)	364	351	206	11575	27273			11575	27273
614 Inflamm dis ovary, fallopian tube, pelvic cellular tissue & peritoneum	159	129	62	5056	10023	50	7540	2528	5012
615 Inflammatory dis uterus, except cervix	16	18	8	509	1399	50	954	254	699
616 Inflammatory dis cervix, vagina & vulva	204	217	46	6487	16861	50	11674	3244	8430
628 Infertility, female	33	89	31	1049	6915	1	80	10	69
633 Ectopic pregnancy	13	14	6	413	1088	43	646	178	468
							20893	6214	14678
Total female consultations							**43518**	**16486**	**27033**
All consultations (male and female)							**66144**	**25637**	**40598**

Male population aged 16-24 = 333 000, Female population = 318 000

Male population aged 25- 44 = 778 000, Female population = 777 000
Source: Population trends, 1998

Consultation rates by age group obtained from MSGP4 for England and Wales are assumed to apply to Scottish population

Cases of Chlamydia reported by GUM clinics in Scotland, persons aged 15 -44yrs

Age group	Male	Female	Total
15-19	141	562	703
20-24	442	561	1003
25-34	509	323	832
35-44	137	61	198
	1229	1507	2736

Source: ISD, Edinburgh: Scottish Health Statistics (http://www.show.scot.nhs.uk/isd/publications/pubss-v.htm) – referenced September, 2000

Estimation of uncomplicated and complicated cases of Chlamydia – assuming proportions observed in England and Wales apply to Scottish epidemiology

- 46% of all male cases due to uncomplicated
- 67% of all female cases due to uncomplicated

When these proportions are applied to figures in table above, the results are shown below:

	Male	Female	Total
Uncomplicated			
15-19	65	377	441
20-24	203	376	579
25-34	234	216	451
35-44	63	41	104
	565	1010	1575
Complicated			
15-19	76	185	262
20-24	239	185	424
25-34	275	107	381
35-44	74	20	94
Total	664	497	1161

Estimation of productivity loss due to Chlamydia managed in GUM clinics

Number of persons	Male	Female	Total
Uncomplicated	24024	28710	52734
Complicated	28225	14078	42303
Total	52249	42788	

Total number of cases reported to ISD			
Number of persons	Male	Female	Total
Uncomplicated	565	1010	1575
Complicated	664	497	1161
Total	1229	1507	2736

Uncomplicated	Male	Female
Full-time	339	414
Part-time	17	172
Complicated		
Full-time	398	204
Part-time	20	84

The following rates of employment were applied to the above figures (Population trends, 1998)

Rates of employment		
	Male	Female
F/t	60	41
P/T	3	17

Assumptions

Uncomplicated	1 day lost for full time employees
	1/2 day lost for part -time employees
Complicated	3 days lost for f/t employees
	1 1/2 days lost for p/t employees

Number of days	Male	Female
Uncomplcated	347	500
Complicated	1225	738
Total days	1573	1238

Average earnings applied to estimates (Earnings Survey, 1998)

Male average daily earnings	81.74
Female average daily earnings	59.44

Estimation of Chlamydia cases presenting in General Hospitals, Scotland

Day cases = 1 lost day of productivity for f/t and 1/2 day for p/t females
Ordinary admissions = avg length of stay + 5 days for f/t, and 1/2 this for p/t
Exclude cases of conjunctivitis (infants)
F/t and p/t employees avg earnings are equivalent
female population aged 15-44 in Scotland = 1 095000

% of population due to OA or DC - based on E&W data	
OA	DC
0.008	0.001
0.059	0.017
0.001	0.091

Number of cases presenting in General Hospitals, England

	Ordinary admissions	Mean duration (days)	Day cases
Salpingitis & oophoritis	89	5.1	14
Inflamm dis pelvic...	648	3.1	188
Infertility, female	8	1.5	991

The assumptions outlined above were applied to this table and combined with Scottish population to produce the following results:

			Lost productivity	
Ordinary admissions	f/t	p/t	f/t	p/t
Salpingitis & oophoritis	36	15	368	76
Inflamm dis pelvic...	266	110	2151	446
Infertility, female	3	1	21	4
			2540	527
Day cases				
Salpingitis & oophoritis	6	2	6	1
Inflamm dis pelvic...	77	32	77	16
Infertility, female	406	168	406	84
			489	101
Total number of productivity days lost				3657
Total cost of productivity days lost				217,380

Chapter 8 – Regression analysis results

	B	S.E.	Wald	df	Sig.	Exp(B)
MSM	-6.697	39.423	.029	1	.865	.001
MSS	.807	.810	.992	1	.319	2.240
EDUUN	.217	1.412	.024	1	.878	1.242
EDUOA	.345	1.325	.068	1	.795	1.412
RACEW	1.651	1.441	1.313	1	.252	5.214
RACEB	1.768	1.504	1.381	1	.240	5.858
EM	-.388	.736	.278	1	.598	.678
AGE1SI	-.285	.156	3.329	1	.068	.752
CPILL	.412	2.066	.040	1	.842	1.510
CCON	-.326	.829	.155	1	.694	.722
CCAP	-7.296	73.129	.010	1	.921	.001
CFE	1.372	2.120	.419	1	.517	3.945
CIUCD	-.286	1.915	.022	1	.881	.751
CO	-8.584	43.636	.039	1	.844	.000
CNONE	-8.741	58.307	.022	1	.881	.000
CCONT	1.170	72.426	.000	1	.987	3.223
CCONECON	-.272	2.187	.015	1	.901	.762
MENL3M	.007	.136	.002	1	.962	1.007
MENNL3M	-.081	.502	.026	1	.872	.922
MENLY	-.031	.226	.018	1	.892	.970
MENL5Y	.086	.090	.920	1	.337	1.090
HSTINF	-.827	.736	1.261	1	.262	.438
SVD	2.013	.971	4.297	1	.038	7.487
SPPU	1.086	1.323	.674	1	.412	2.964
SPUMOTN	-.064	.842	.006	1	.939	.938
SPLA	-.671	1.362	.243	1	.622	.511
SBBP	-7.410	134.998	.003	1	.956	.001
SBAS	-5.959	135.001	.002	1	.965	.003
SPDS	-1.449	1.200	1.459	1	.227	.235
SNONE	-5.702	177.220	.001	1	.974	.003
PPULADS	-.103	1.559	.004	1	.947	.902
BBPOAS	7.155	135.006	.003	1	.958	1280.221
CSYMP	-6.800	177.223	.001	1	.969	.001
PWHOP	.341	.815	.175	1	.676	1.406
PWHCGS	1.371	.666	4.237	1	.040	3.938
Constant	4.325	191.472	.001	1	.982	75.579

a Variable(s) entered on step 1: MSM, MSS, EDUUN, EDUOA, RACEW, RACEB, EM, AGE1SI, CPILL, CCON, CCAP, CFE, CIUCD, CO, CNONE, CCONT, CCONECON, MENL3M, MENNL3M, MENLY, MENL5Y, HSTINF, SVD, SPPU, SPUMOTN, SPLA, SBBP, SBAS, SPDS, SNONE, PPULADS, BBPOAS, CSYMP, PWHOP, PWHCGS.

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