

# HOSPITAL ACQUIRED INFECTION

HAI



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## Erratum

Figure 1 on page 18.  
The pie chart segment  
labelled "*Skin 11%*" should  
read "***Blood Stream 11%***"



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# CONTENTS

1	Introduction	5
2	Historical background	7
3	Aetiology of HAI	11
4	Prevalence, incidence and impact on mortality of HAI	15
5	Prevention of HAI	21
6	Organisation, costs and management of infection control	25
7	The economic evaluation of HAI	30
8	Conclusion	45

## Figures

<b>Figure 1</b>	The frequency of infections by site of infection	18
<b>Figure 2</b>	Classification of costs	32

## Tables

<b>Table 1</b>	Main groups and pathogens associated with HAIs	12
<b>Table 2</b>	Prevalence of HAI per 100 patients by country, year of study and number of hospitals and patients included	16
<b>Table 3</b>	Ten leading causes of death in the United States in 1982 by cause of death	19
<b>Table 4</b>	Results of cost-of-illness studies of HAI by type of infection, length of stay and extra costs or charges 1978-1994	38
<b>Table 5</b>	Yearly costs and benefits of an infection control programme in an average 250 bed hospital in the US assuming 3 possible levels of programme efficacy	42

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# 1 INTRODUCTION

'About one in ten patients in acute hospitals at any one time has an infection acquired after admission to hospitals' (DH/PHLS, 1995, p1). This quotation, introducing recent guidance on the control of infection in hospitals, gives us some indication of the size of the problem and the reasons for concern about the risks to health and the demands on scarce resources engendered by potentially reducible hospital acquired infection (HAI). HAI or nosocomial infection has been described as an infection, not present on admission, but acquired during a stay in hospital, that manifests itself either during the stay in hospital or in the period following a hospital stay (Haley, 1986). The main types are urinary tract infections (UTI), surgical wound infections (SWI) and respiratory tract infections (RTI). Estimations of the costs of HAI to the health sector vary depending on the type of infection, age of the patient and the type of costs included in the study (DH/PHLS, 1995). Coello *et al.* (1993) estimated the mean extra cost of treating a patient with a UTI to be £467 and the extra cost associated with treating a patient who acquired a SWI or more than one infection to be £1,454 and £3,362 respectively. Pittet *et al.* (1994) estimated the cost per case of septicæmia to be £25,753. The national burden of HAIs occurring in surgical patients was estimated to be over £170m to the hospital sector in England (Coello *et al.*, 1993). Costs that fall outside the hospital sector and impose burdens on community services, patients and their families have not been included. It has been estimated that approximately 30 per cent of HAIs can be prevented (Haley *et al.*, 1985b).

Infections acquired in hospitals are likely to complicate illness, cause discomfort and anxiety and can lead to death. Resources are required to implement infection control programmes and to diagnose and treat patients. The former include the costs of specialist doctors, nurses and microbiologists employed to prevent and control infection and undertake surveillance, and the costs associated with diagnostic tests and prophylactic interventions that are undertaken whether an infection occurs or not. The hospital infection control team is used to identify certain infections, prevent secondary cases occurring and control outbreaks. Additional help may be needed from specialists in infectious disease control in the community and sometimes from experts in national centres of disease control. Health sector resources are used to diagnose and treat patients who acquire an infection during their hospital stay. Patients, families and industry may also experience additional costs



resulting from the impact of infection. The costs of infection are thus distributed amongst hospitals, community services, patients, their families and industry. The distribution of these costs will depend to some extent upon the organisation of the health care system, admission and discharge policies and the interface between primary and secondary care. Given that many health care systems are changing, that lengths of stay are shrinking and that financial accountability is both more transparent and more stringent, it is not surprising that the financial implications of HAI are of particular contemporary interest.

Economic evaluation has a role to play in the policy for and management of HAI. It can help to determine the cost-effectiveness of alternative regimes for controlling and managing infections within hospitals, and the cost-effectiveness of particular types of interventions to prevent infection occurring or limit its spread. However, economic evaluations in the area of HAI are fraught with problems related to case definition, detection and the attribution of the costs to the infection. These issues will be reviewed below.

The next section of this report sets the historical context for discussion of HAI, which has been recognised for centuries. This is followed by a description of the aetiology, prevalence and incidence of HAI and its impact on mortality. The strategies that might be employed to prevent infections are briefly discussed; and an outline is given of the organisational arrangements to control infection in hospitals and the costs likely to be associated with such arrangements. Economic evaluative studies are then reviewed in the light of the methodological issues that are encountered by analysts undertaking work in this area. Gaps in our knowledge are indicated and policy implications are considered.

## 2 HISTORICAL BACKGROUND

Some of the earliest references to HAI are found in the writings of classical Greek scholars. This historical material was reviewed by La Force (1987) and Glenister (1991). Most references attribute a cause and suggest a preventive strategy accordingly. One of the earliest explanations suggested is the 'miasma' theory. This is based on the belief that fetid air was laden with poisons and products of putrefaction. Hippocrates provides us with one of the earliest references to such effects. More recently, in the eighteenth century, Pringle (1752) advocated better ventilation to rid wards of 'corrupted air'. He observed that wards with broken windows had lower rates of infection and advocated the use of chimneys which would act as ventilation shafts. Howard (1789), who reviewed hospitals in both England and abroad, noted dirty floors and stuffy environments and recommended airy, eight bedded wards. Clare (1779) observed better recovery after surgery in country hospitals than hospitals in London. Simpson (1869) advocated a shorter pre-operative stay to minimise the exposure of patients to 'vitiating' air and undertook a survey of 400 practitioners throughout Britain. He confirmed Clare's view and recommended that hospitals should be small and rebuilt every few years to counter 'hospitalism', a nineteenth century term for HAI. Others also advocated the destruction of hospitals, 'the truth is that, once a hospital has become incurably pyaemic-stricken, it is impossible to disinfect it by any known means, as it would be to 'disinfect' a crumbling wall of ants that have taken possession of it...' (Godlee, 1924 p136). This view that the infection permeated the building was also found in other examples. Nightingale (1863) challenged the concept of hospital design and advocated improvements that included more ventilation and smaller wards.

Nightingale saw the problem of HAI as being associated with the congregation of large numbers of persons in one room, thus espousing contagion theories which also had a long history as the cause of the problem. This was one of the causes identified by Francastoro in the sixteenth century, who postulated three 'seeds' of disease by contagation: contagation by contact; contagation by inanimate objects and contagation at a distance. This early description of the cause of infection has its echoes in present day theories described below. Others to advocate the reduction of contagation include Lind, a naval surgeon in the eighteenth century, who advocated separate wards for different infectious diseases.



Tenon also acknowledged that the infection was passed from person to person and recommended separate wards and a preparation ward attached to the operating theatre (Glenister, 1991). Current procedures to prevent spread of infection and to protect the vulnerable and immunologically impaired people reflect the continuing importance of this mode of prevention and control with patients being isolated when necessary and the appropriate precautions taken.

Another form of attack on infection concentrated upon the site of the wound. The idea that the discharge from wounds was part of the process of infection, led to the encouragement of the formation of 'laudable pus' that was thought to form part of the healing process. There were however challenges to this view, it was suggested that pus was part of the problem, rather than the solution, even in the early middle ages. Few remedies were advocated. Treatment with egg yolk, oil of roses and turpentine in the sixteenth century were some of the earliest examples (Glenister, 1991). Treatment with maggots was also advocated (Rowbotham, 1995; Sherman *et al*, 1988). Lister's preparation of the site of an incision and the treatment of the wound with powerful antiseptic was an important step forward in the reduction of infection (Lister, 1867). Lister's intervention was the product of clinical and biological investigation (Godlee, 1924). Unlike some of his contemporaries who were undertaking statistical prevalence studies, he refused to publish his results in statistical form, preferring a case by case assessment of his methods. He recognised the likelihood of interpretation problems that we might now see as problems of definition, differences in case mix and small numbers. Semmelweiss, using a statistical approach in what transpired to be a natural experiment, observed that fewer women died of puerperal fever when treated by midwives than when treated by medical students (La Force, 1987). The full significance of the statistical material was found when it was observed that a colleague, wounded through a needle stick injury whilst undertaking a post-mortem, died of sepsis. Students often went straight from the post-mortem room to deliver babies. Semmelweiss concluded that the cause of puerperal fever and septicaemia was the same and suggested a prevention measure that has stood the test of time: hand washing. Farr and Nightingale were keen to introduce a statistical approach to infection advocating better record keeping in particular the publication of mortality rates. The statistical information provided by Farr, on mortality rates in large and small hospitals, met with severe criticisms relating to the method of collection and interpretation. In particular Farr was

criticised for not adequately accounting for the 'length of stay' of patients in hospital. Despite these early criticisms a more systematic approach to the epidemiology of HAI was not firmly established until the early 1950's (La Force, 1987).

The idea that the health care worker could transfer disease is still a major source of concern today, especially in relation to the spread of blood borne infections such as HIV and hepatitis and the emerging problem of resistant organisms. This theory of infection led to the introduction of gloves and masks to protect doctors, nurses and patients (Halsted, 1913). It also contributed to the introduction of training for nurses and the development of a nursing profession (Nightingale, 1863; Abel-Smith, 1960).

Speculation of the role played by germs evolved from Fracastro's proposition of the existence of 'seeds,' through Kircher's discovery of the 'masses of small worms' in the seventeenth century, to the development and identification of organisms that caused specific diseases by Koch and others at the end of the nineteenth century. This work, and subsequent refinements leading to the introduction of microbiological explorations, has provided the basis for our present understanding of infections. This march of biological, micro-biological and later virological findings in the twentieth century has led to several complementary approaches to dealing with infection: preventing infections through aseptic procedures during invasive and related procedures; prophylactic antibiotics to protect patients likely to be exposed to, or particularly vulnerable to, infection; and treatment of infections that arise with antimicrobials.

There is no specific historical account of the economic concerns relating to hospital infections. The importance placed upon economic and financial aspects of HAI can, however, be gleaned from discussions found in the diverse literature on hospitals. It was suggested, in hospital reports reviewed by Croxson (1995) for example, that budgetary restrictions were preventing regular maintenance work and cleaning from being carried out in a London Hospital in the 18th century. As hospital conditions were already implicated as encouraging infection these cut backs were likely to have reflected badly on the hospital. Croxson (1995) also indicates that infections, or a reputation for infections, were seen as likely to have adverse effects on the use of a hospital and provide the motivation for the growth in dispensaries. Infection was bad for business. The use of hospitals in general was also questioned, 'what beneficent effects such institutions may have had were almost certainly more than counter balanced by the dissemination among

their inmates of those dangerous germs' (Heilliner, 1957 p6). However, this view was not universally held and some pointed to the low mortality rates from hospital infection in the late 18th century. There is also an indication that conditions in voluntary hospitals were sometimes better than in municipal hospitals. In the late nineteenth century, University College Hospital, London, was seen to be on a par with the Boston General Hospital and considerably superior to Parisian hospitals in the mortality rates experienced by amputees. University College Hospital had a 26 per cent mortality rate amongst amputees, compared to a 60 per cent mortality rate observed amongst amputees treated at Parisian hospitals. Infection was seen as a major factor contributing to this mortality. This is an early example of the use of performance league tables to indicate the superiority of a hospital in the field of infection control (Godlee, 1924 p132/3). However, care must be taken in interpreting infection rates as case mix and definitions of HAI differ widely between studies and hospitals. Some of the early advances in treating infection were criticised for being more costly than allowing people to die as they involved a longer hospital stay. Lister had to confront angry managers about the length of time his patients remained in hospital (Roberts, 1995).

Increasingly HAI is viewed from the perspective of the burden that it imposes on scarce resources. The assessment of the economic burden of infection requires an understanding of the nature of HAI, its aetiology, prevalence and the likely interventions that can limit its spread. Let us begin by considering its aetiology.



## 3 AETIOLOGY OF HAI

### Introduction

Infection occurs when a micro-organism invades a susceptible host and causes disease. If the micro-organism is a commensal organism, ie. it already resides in the host, an infection may develop as a result of a change in the relationship between the micro-organism and the host. The interaction between micro-organisms, the route of transmission and the host is called the chain of infection. In this chapter the various components of the chain are reviewed with specific reference to HAI.

### Micro-organism/pathogen

A micro-organism that leads to a disease state in an individual is called a pathogen. It can be a bacterium, a protozoan, a virus or a fungus. The vast majority of HAIs are caused by bacteria. The pathogenicity of an organism directly refers to the ability of the organism to cause disease. Pathogenicity varies considerably among the diverse members of the microbial world and not all pathogens have an equal probability of causing disease in the same population. For example, *Staphylococcus aureus* (*S. aureus*) is a major pathogen responsible for between 10 and 20 per cent of HAI, and has relatively high pathogenicity compared to *Staphylococcus epidermidis* (*S. epidermidis*), a member of the same bacterial genus (Micrococcaceae). *S. epidermidis* is a normal skin commensal and rarely associated with significant infection in a non-susceptible host. Differences between these organisms include the presence of specific virulence factors produced by *S. aureus* that enhance its potential ability to cause disease.

Virulence refers to the degree of pathogenicity of an organism and may be described by reference to epidemiological measures such as morbidity, mortality and communicability, or by clinical factors characterising the severity of the infection observed. Organisms such as *S. aureus*, *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* can be regarded as principal pathogens. They regularly cause disease in immunocompetent individuals. However, when considering the aetiological agents involved in HAI, a considerable number of non-principal organisms are implicated. *Pseudomonas aeruginosa*, *Enterococcus faecalis* and indeed *S. epidermidis* are major causes of HAI and yet rarely cause disease in people with intact host defences. Such organisms can be regarded as opportunists. This opportunism is a direct result of hospitalised individuals being more

**Table 1 Main groups and pathogens associated with HAIs (expressed as percentages of groups and pathogens)**

Groups and main pathogens	%
<b>Groups</b>	
Gram – negative bacteria	50.7
Gram – positive bacteria	37.5
Anaerobes	2.9
Other micro-organisms	8.9
<b>Main pathogens</b>	
<i>Escherichia coli</i>	16.3
<i>Pseudomona aeruginosa</i>	11.5
<i>Proteus mirabilis</i>	3.7
<i>Staphylococcus. aureus</i>	11.2
<i>Enterococcus spp</i>	7.7

Source: Compiled using data from EPINE Working Group (1992).

likely to lack an intact innate or acquired immune system and are therefore a more susceptible population. Table 1 illustrates the main groups and pathogens implicated in HAI.

## Route of transmission

There are four main routes of transmission: contact, common vehicle, airborne and vector borne.

Contact can be direct or indirect contact. Direct contact involves the source and host coming into physical contact with each other allowing for direct transfer of micro-organisms. Indirect contact refers to the passive transfer of micro-organism from the source to the host usually via hands or inanimate objects.

Common vehicle transmission involves a single inanimate object such as food or water, which serves to transmit the micro-organism to several individuals. The vehicle may be actively involved in transmission, the micro-organism multiplying within the vehicle, or passively involved serving only as a means to transmit the micro-organism.

Airborne transmission involves the transfer of micro-organisms through the air from source to host either in the form of droplet nuclei or on dust or skin cells.

Vector borne transmission refers to the transmission of micro-organisms via insects and is relatively unusual in industrialised countries.



Most pathogens have one known route of transmission. However some micro-organisms can be spread by a number of routes. For example, *Salmonellae* are usually transmitted by a common vehicle, but can also be transmitted by vectors.

## Host

Individuals are protected from microbial invasion by non-specific and specific defence systems. The non-specific defence system includes the skin, mucous membranes, certain bodily secretions and the inflammatory response. The intact skin provides a tough outer layer which few microbes can penetrate. Anti-bacterial substances, present in the sweat and the secretions of the sebaceous glands, add further protection and microbes normally found on the skin (e.g. *S. epidermidis*), protect against invasion by pathogens through competition for nutrients. Any break in this protective barrier, such as an open wound, will provide a portal of entry. The mucus membranes of the respiratory tract produce mucus which traps particles that enter the airway. The cilia then move the mucus upwards to the oropharynx where it is swallowed or expectorated. Lysozyme, present in tears and saliva, is capable of lysing bacterial cell walls especially those of Gram positive bacteria. Finally, the inflammatory response, classically characterised by redness, heat, swelling and pain at the site of invasion, represents the initiation of the specific defence system. This system comprises the humoral and cellular arms of the immune system. Both may be acquired naturally through infection or artificially through vaccination.

Within the hospital environment individuals are exposed to greater microbial risk than in the community. On admission to hospital the normal skin flora are often replaced by strains of hospital bacteria which are more resistant to antibiotics and can cause serious infection if they enter the body. Medical or surgical therapy often requires therapeutic interventions that breach the natural defence mechanisms providing a portal of entry for invading micro-organisms. Surgical procedures and intravenous therapy result in a break in the integrity of the skin. Micro-organisms may enter the urinary tract during the process of catheterisation or instrumentation, or they may travel retrogressively through or along a urinary catheter. The protective action of the mucous membranes and cilia of the lungs may be inhibited by drugs, or bypassed in a ventilated patient by an endotracheal tube, providing a direct route of entry for micro-organisms.

The presence of a portal of entry does not necessarily result in the

development of an infection. The development of an infection is dependent on the pathogenicity of the invading agent and the susceptibility of the host. The very young are particularly susceptible since their immune system is in an immature state. The elderly are similarly at greater risk since their immune system is less efficient. Individuals with illnesses that affect the immune system such as leukaemia and AIDS are by definition immunosuppressed and may be rendered more susceptible by the toxic effects of the therapy they receive.

## **Environment**

Environmental factors such as temperature, air movement and the presence of chemicals, gases and toxins may have an effect on any of the factors involved in the development of infection. Particular environmental factors may limit, inhibit or prevent the development of an infection. For example, environmental factors such as temperature and humidity may promote or inhibit the growth of micro-organisms in their reservoir. Movement and velocity of the air may affect transmission of micro-organisms from source to susceptible host.

The next chapter will consider the prevalence and incidence of HAI and their impact on mortality.

## 4 PREVALENCE, INCIDENCE AND IMPACT ON MORTALITY OF HAI

### Introduction

Quantifying the occurrence of HAI and its impact on mortality is difficult for a number of reasons. The presence of HAI is often not accurately and routinely recorded; there are variations in the way infection rates are measured; the criteria used for defining infections vary considerably; methods used for detecting a case of infection differ; it is difficult to control for case-mix differences; and determining the impact that HAI has on mortality is extremely difficult. Nevertheless, studies indicate that HAI is a significant problem in terms of prevalence, incidence and impact on mortality.

### Prevalence

Prevalence data measure the proportion of individuals in a population who have a HAI at a specific instant in time, for example, the number of patients with an active HAI expressed as a percentage of the total number of patients studied. Such data provide an important insight into the scale of the problem. However, since prevalence data refer to a single point in time, they can be subject to bias arising from outbreaks of infection or seasonal variations. Furthermore, since prevalence data refer to infections present amongst hospital populations at the time of survey, infections that present post-discharge are excluded so the scale of the problem may be underestimated.

Many prevalence studies have been conducted. The findings of some of these studies are set out in Table 2. Although there are clearly differences between the findings of these studies they are perhaps more remarkable for their similarities. HAI is generally found to have a prevalence of around 10 per cent. Much of the variation can be explained by differences in methodology employed and differences in case-mix and clinical practice.

Although the overall prevalence of HAI is approximately 10 per cent there is considerable variation amongst subgroups of patients. For example, prevalence rates vary with age and specialty. Much of this variation can be explained by reference to the particular case-mix characteristics of the subgroup in terms of risk factors for infection.

**Table 2 Prevalence of HAI per 100 patients by country, year of study and number of hospitals and patients included**

Country	First author and date of publication	Year of study	No. of hospitals studied	No. of patients studied	Prevalence of HAI per 100 patients
Sweden	Bernander (1978)	1975	5	3,657	10.5
Denmark	Jepsen (1980)	1978	25	1,363	10.4
Denmark	Jepsen (1980)	1979	25	1,557	12.1
Norway	Hovig (1981)	1980	15	7,833	9.0
England & Wales	Meers (1981)	1980	43	18,163	9.2
Italy	Moro (1983)	1983	130	34,577	6.8
14 countries, WHO	Mayon-White (1988)	1983-85	47	28,861	8.7
Australia	McLaws (1988)	1984	269	28,643	8.1
Czechoslovakia	Sramova (1988)	1988	23	12,260	6.1
Thailand	Danchaivijitr (1989)	1988	23	6,805	11.7
Hong Kong	Kam (1993)	1987	10	9,848	8.6
Spain	EPINE Working Group (1992)	1990	123	38,489	9.9
France	Sartor (1995)	1992	8	1,220	8.6
France	Sartor (1995)	1992	8	1,389	7.1
UK & Republic of Ireland	Emmerson (1996)	1993-94	157	37,111	9.0

Source: Compiled from the literature reviewed.

## Incidence

There are two specific measures of incidence: cumulative incidence and incidence density or force of morbidity.

Cumulative incidence measures the proportion of people who acquire an HAI during a specified period of time. For example, the number of new cases of HAI occurring over a specified period of time expressed as a percentage of the total number of patients discharged during the period of study.

Incidence density or force of morbidity measures the number of new cases of HAI occurring during the period of survey and expresses this figure as a proportion of the time each patient remained in hospital free from infection during the same time period. That is the number of days from time of admission to either time of discharge in the absence of a HAI, or where a HAI is present the day of onset of that HAI. The incidence rate can therefore be interpreted as the risk of developing a HAI per unit of time exposed. This measure of the incidence of HAI overcomes some of the



confounding effects of length of stay. Hospital length of stay will vary, both within and between hospitals, depending on factors relating to case-mix and discharge policies and this will inevitably have an impact on the HAI rates observed. If the mean length of stay is relatively short, the number of discharged patients will be relatively high and as a result the cumulative incidence rate may appear low, whereas in situations where the mean length of stay is relatively long the opposite may occur.

A number of studies have attempted to estimate the incidence of HAI. The majority of these studies have focused on specific patient groups, or specific infections. For example Moir-Bussy (1984) examined the incidence of HAI following caesarean section; Crow (1988) the incidence of UTIs in catheterised patients and Meers *et al.* (1990) the incidence of methicillin and aminoglycoside resistant *S. aureus* in a teaching hospital. These incidence studies provide important information of particular relevance to health care professionals caring for similar patients. However, it must be noted that only those infections that present during the hospitalised period were included in the incidence rate and as such the incidence rate observed may underestimate the actual incidence of HAI in the selected patient group.

A few studies have attempted to estimate the incidence of all types of HAI. Perhaps the most notable of such studies is the Study of the Efficacy of Nosocomial Infection Control (SENIC) conducted in the US. This study investigated the incidence of all HAI over a prolonged period of time in 338 hospitals, representing the 6,449 acute sector hospitals in the US. The incidence of all HAI was found to be 5.7 per cent (Haley *et al.*, 1985b). Infections presenting post-discharge were not included.

More recently Glenister *et al.* (1992) studied the incidence of HAI occurring in patients admitted to medical, surgical, urology, gynaecology and orthopaedic units at a district general hospital in the UK and found the incidence to be 9.2 per cent. Again, infections presenting post-discharge were not included.

As with prevalence studies, the overall incidence rates conceal the considerable variation that is present when particular subgroups are examined. For example, Glenister found that the incidence varied from 7.2 per cent amongst patients admitted to the medical speciality to 13.4 per cent amongst patients admitted to the orthopaedic speciality.



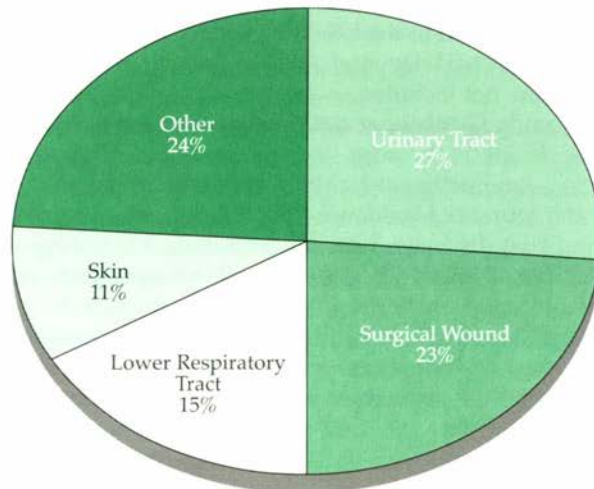
## HAI presenting post-discharge

Prevalence studies fail to take into account infections that present post-discharge and incidence studies rarely include such infections. The literature on this topic suggests that HAI presenting post-discharge is a significant problem. Holtz in a review of the literature found that between 20-70 per cent of surgical wound infections do not present until after discharge from hospital (Holtz *et al.*, 1992). Little is known about the incidence of other types of HAI post-discharge. Many health care systems are experiencing a change in discharge policies, with patients being discharged into the community earlier. Since length of stay is a risk factor for infection, this policy could possibly result in a reduction in the infection rate. However, unless infections presenting post-discharge are included in the incidence rates, it will not be clear to what degree rates have been reduced. The move towards shorter lengths of stay may well be accompanied by an increase in the number of infections presenting post-discharge.

## The types of HAI

Urinary tract infections (UTI) are the most common types of infection, with surgical wound infections (SWI) and lower respiratory

Figure 1 The frequency of infections by site of infection



tract infections (LRTI) consistently comprising the other major groups (see Figure 1). The relative frequency of other types of infections has been found to differ depending on the case-mix of the sample studied.

## Mortality attributed to HAI

Data from prospective hospital studies, collaborating in a Center for Disease Control study in the US, suggest that of those patients who acquire an infection in hospital, 10 per cent will subsequently die in hospital (Haley, 1986). HAI is directly responsible for 10 per cent of these deaths and is a major factor in a further 30 per cent. When these figures were extrapolated to the more than 2 million HAI occurring annually throughout the US, it was estimated that in 1982, 20,000 deaths were attributable to HAI and a further 60,000 deaths partially attributable to HAI. The magnitude of these figures can be understood by comparing them to the all cause mortality statistics for the US (See Table 3). If only those deaths directly attributable to HAI are considered, HAI is the 11th leading cause of death. If deaths directly and partially attributable to HAI are considered, HAI is the 4th leading cause of death.

*Table 3 Ten leading causes of death in the United States in 1982*

Rank	Cause of death	Estimated number of deaths
1	Heart Disease	756,000
2	Cancer	434,000
3	Stroke	158,000
X	HAI constituting main cause of or contributing importantly to death	80,000
4	Chronic lung disease	59,000
5	Pneumonia and influenza	49,000
6	Motor vehicle accidents	49,000
7	Other accidents	46,000
8	Diabetes mellitus	36,000
9	Suicide	28,000
10	Chronic liver disease	28,000
XX	HAI constituting main cause of death	20,000

Source: Haley, (1986)

Equivalent data are not available for the UK. However, assuming a similar mortality rate, it has been calculated that in 1993, 5,000 deaths might be primarily attributable to HAI and in a further 15,000 cases HAI might be a substantial contributor (DH/PHLS Hospital Infection Working Group, 1995). If this is the case HAI is a more common primary cause of death than road traffic accidents or suicides.

## 5 PREVENTION OF HAI

Although not all HAI can be prevented, there being an ‘irreducible minimum’ (Ayliffe, 1986), it has been estimated that approximately one third of these infections may be prevented through effective infection control (Haley *et al.*, 1985b). This chapter considers some of the principles of infection control.

### Principles of infection control

Infection control aims to reduce the number of infections occurring by reducing the risk of transmission of potentially pathogenic organisms from their source to the host; limiting their impact once they have entered the host; and minimising the spread of an established infection from patient to patient, patient to staff and vice versa.

Infection control practices may be categorised as specific and non-specific. The latter include practices routinely carried out in the care of all patients which aim to reduce the transmission of micro-organisms. For example, sterilisation procedures, hand washing, the use of protective clothing and the careful disposal of body fluids. Other procedures are more specific to the particular treatment and care an individual patient receives. For example, specific care related to in-dwelling devices such as urinary catheters, intravenous lines and wound drains; wound care and the use of prophylactic antibiotics which aim to prevent infections.

The efficacy of particular infection control practices has been well documented. A plethora of research literature exists on, for example, the effectiveness of hand washing as a means of reducing transmission of micro-organisms (e.g. Larson *et al.*, 1988; Reybrouck, 1983) and the importance of the use of closed drainage systems with in-dwelling urinary catheters (e.g. Thornton *et al.*, 1970). There is, however, considerable evidence that important infection control procedures are often not adhered to, for example, medical and nursing staff are often complacent about hand washing practices (Graham, 1992; Gould, 1994).

### The importance of surveillance

Surveillance involves the collection and analysis of data on infections occurring in patients and staff, and dissemination of the results to the relevant personnel so that appropriate action can be



taken. The main objectives are the prevention and early detection of outbreaks of infection in order to facilitate investigation and control, and the measurement of the incidence of HAI over time, in order to determine the effectiveness of preventative and control measures and adjust practice as necessary. Data from a study of 338 US hospitals highlight the importance of surveillance (Haley *et al* 1985b). The incidence of HAI over a five year period was found to decline substantially in those hospitals with active surveillance and control programmes, whereas hospitals without such activities saw an increase in their infection rates (Haley, 1986). Surveillance activities were found to have had an impact on infection rates which could not be explained by other infection control practices and the authors concluded that without organised routine surveillance infection control policies are unlikely to be fully successful.

There are a variety of different ways of conducting surveillance. In the UK, a recent survey by Cookson indicated that 'alert organism' surveillance appears to be the method of choice with 95 per cent of the 185 infection control teams questioned practising this form of surveillance (Cookson, 1995). 'Alert organism' surveillance involves restricting data collection to information on particular micro-organisms that are liable to give rise to outbreaks, such as: MRSA, other highly resistant *S. aureus* strains, Legionella species and *Clostridium difficile*. On a daily basis infection control teams are informed of the presence of 'alert' organisms. Outbreaks are suspected when two or more indistinguishable organisms are isolated from different patients in the same ward or unit. On identification of a possible outbreak appropriate action is initiated. The extent and cause of the outbreak, if present, is established and the necessary control measures introduced and enforced.

This form of surveillance has the advantage of being a relatively easy and effective method of rapidly detecting infection or colonisation on a hospital wide basis. However, for several reasons, including failure to take appropriate specimens or negative laboratory results being obtained due to patients being treated with antibiotics, this method lacks a degree of sensitivity. A DH/PHLS report recommends that 'alert organism' surveillance should be carried out in all hospitals together with: 'alert condition' surveillance; continuous surveillance of microbiology specimens and results in an endeavour to identify outbreaks and changes in patterns of infection; and targeted and selective surveillance to monitor trends in infection in specific patient groups or in specific areas within the hospital (DH/PHLS, 1995). 'Alert condition' surveillance relies on ward staff reporting conditions such as diarrhoea and



meningitis to the infection control team. The infection control team then acts on this information. Targeted surveillance refers to the collection of data on HAIs occurring in selected patient groups. Selective surveillance refers to surveillance methods which do not aim to identify every infection but rather aim to identify the majority of infections.

The need for surveillance has been further highlighted in a recent report on HAI surveillance policies and practice (Glynn *et al.*, 1997). This report recommends that all hospitals should have a formal system of surveillance for HAI and that surveillance should concentrate on specific objectives. A national surveillance system (Nosocomial Infection National Surveillance System – NINSS) is currently being set up in England. Participating provider units will be asked to collect data on selected HAIs, together with information on key risk factors and relevant denominator data, using defined protocols. This information will be analysed by the Nosocomial Infection Surveillance Unit (NISU). Rates adjusted for case mix will be fed back to provider units, together with aggregated anonymised data from other provider units. This system will therefore enable participating hospitals to compare their own infection rates with aggregated, anonymised data from other hospitals, thereby providing information that may be used to inform infection control practice.

## The use of antibiotics

Antibiotics are used both in the treatment of HAI and as a means of prevention through their prophylactic administration. Discovered in the late 1930s, antibiotics have revolutionised health care. Prior to their discovery infections were rampant and surgical procedures were fraught with danger. Their introduction has led to safer medical and surgical practice and prolongation of life expectancy. However, caution must be taken when prescribing these drugs. Antibiotic resistance is a growing problem. Bacterial evolutionary responses to the selective pressure of antibiotics have resulted in micro-organisms resistant to virtually every known antibiotic. For example, in 1941 virtually all strains of *S. aureus* were sensitive to penicillin. Within three years of its introduction several strains of *S. aureus* became capable of  $\beta$  lactamase production thereby inactivating the drug and removing the drug's clinical efficacy. In an endeavour to overcome this specific resistance problem, semi-synthetic penicillins were produced. Methicillin was the first such penicillin but was superseded by a less toxic derivative

flucloxacillin. Methicillin is however still used for in-vitro sensitivity testing as it has identical resistance patterns to those of flucloxacillin (Duckworth, 1993). Soon after its introduction methicillin resistant *S. aureus* (MRSA) developed (Cetin *et al.*, 1962) and the frequency of isolation of this organism has increased steadily. MRSA strains are resistant to all penicillin derivatives and are in many cases resistant to other antibiotics. Vancomycin is the only consistently effective agent of use clinically. Many other examples of antibiotic resistant micro-organisms can be cited; for example, multiple resistant Gram negative bacilli and vancomycin resistant enterococci.

This chronic and constantly evolving situation has important consequences for clinical practice. Patients infected with a multi-resistant organism suffer increased morbidity and mortality and often require the use of expensive and potentially toxic antibiotic regimes in order to achieve effective treatment (Holmberg *et al.*, 1987). In some cases, for example infections caused by some strains of *S. aureus* and *Mycobacterium tuberculosis*, the emergence of resistance has drastically reduced, and on occasions prevented, effective antibiotic treatment. This situation highlights the need for vigilance in the field of infection control, close adherence to known preventative measures and the need for great care when prescribing antibiotics. Kunin notes that studies which have examined antimicrobial prescribing in hospitals suggest that about half of the antimicrobials prescribed are prescribed inappropriately: that is, antibiotics are either not indicated for the condition or they are incorrectly prescribed (Kunin, 1990). Greater care must therefore be taken when prescribing antibiotics to ensure that the most appropriate antibiotic is prescribed in terms of type, dose and duration of therapy. Appropriate investigations to identify the causative pathogen may facilitate this process. Unless such measures are taken the problem of microbial resistance to antibiotics will continue to escalate.

## 6 ORGANISATION, COSTS AND MANAGEMENT OF INFECTION CONTROL

### Organisational structures

In the UK and indeed many other countries rules and regulations along with a system for implementing public health policies in relation to infection control are in place. In the late fifties and early sixties there was growing pressure for the adoption of 'infection officers' and 'infection control sisters' (LaForce, 1987) with the first infection control nurse being appointed in 1959 (Ayliffe *et al.*, 1990). The majority of hospitals now have an infection control policy that includes regulations about the control of infection and lays down guidance about the day to day management of infection control.

There is recommended guidance about the organisation of the control of infectious disease in England and Wales (DH/PHLS, 1995; Infection Control Standards Working Party, 1993). The overall responsibility resides with the Consultant in Communicable Disease Control (CCDC) for the Health Authority in which the hospital is situated. In hospitals the responsibility lies with the hospital infection control committee (HICC), which reports to the Chief Executive (or their deputy) of the Trust which manages the hospital.

The members of a HICC should include:

- Consultant in Communicable Disease Control (CCDC)
- Infection Control Doctor (ICD)
- Infection Control Nurse (ICN)
- Medical Microbiologist (if the ICD is from a different speciality)
- Occupational Health Physician/Nurse
- Senior Medical and Surgical staff representing their colleagues
- Infectious Disease Physician
- Representative of the Executive Nurse Director
- Chief Executive or representative

The responsibilities of this committee include the provision of appropriate infection control advice, and the formation and review of infection control policies and a programme of action relating to the prevention and control of routine infections and outbreaks of infection.

Infection control policies cover a wide range of activities within the hospital (both clinical and non-clinical) and aim to provide guidance on how the risk of infection may be minimised. Policies may be based on central guidance, for example policies relating to



laundry and linen services; regulations, such as those governing the handling of clinical and non-clinical waste; and good practice.

Policies extend to audit and surveillance procedures and to microbiological services (their availability, reporting practices and role in advising on the control of infection and the storage and retrieval of data). Education policies are also drawn up that relate to the continuing education of the team and the education of all medical, nursing and related staff in infection control procedures and practices. It is recommended that all new hospital staff, cleaners, porters, nurses and consultants, know about the relevant policies within the first seven days of their employment in the hospital.

In addition to policies relating to routine control, detailed guidelines are available to deal with outbreaks of infection. The reporting of notifiable infections to the CCDC is required and the CCDC should be consulted on any major outbreak of infection in the hospital. If an outbreak occurs an outbreak committee is set up. Members of this committee include the CCDC, the ICT, the clinicians concerned, the Chief Executive or a representative and any other relevant persons depending on the nature of the outbreak. This committee is charged with the responsibility of formulating, implementing and regularly evaluating an action plan and modifying the course of actions as necessary. When necessary the expertise of the national advisory agencies of the Public Health Laboratory Service (PHLS) should be sought, including clinical and epidemiological advice and specialist laboratory services.

The day to day implementation of control programmes is the responsibility of the Infection Control Team, (ICT). This team is made up of the ICD, ICN(s) and the medical microbiologist if the ICD is from another specialty. Sufficient ICNs are required to provide an adequate service, along with administrative support and adequate facilities and supplies. The ICT reports directly to the Chief Executive (or deputy) and to the HICC and liaises with the CCDC and, when necessary, with other agencies such as environmental health departments and the Health and Safety Executive. The ICT is concerned with the prevention and control of infections; the identification and control of outbreaks in collaboration with the CCDC and an outbreak control committee; educating staff on the principles of infection control; the establishment of link nurses (identified nurses in each ward with a particular interest in infection control who act as a resource for colleagues and liaise closely with the ICNs); the provision of information on infection control procedures and the provision of expert advice on the care of infected patients on a 24 hour basis.

## Costs of infection control

Estimating the overall costs associated with the prevention and control of HAI is difficult. Activities which aim to prevent infection are thoroughly integrated into every day hospital practice, rendering it almost impossible to separate out all activities associated with the prevention of infection.

The costs of establishing an infection control team are rarely available nor are the costs of all the routine procedures and practices performed by the various people involved in preventing infection. These ex-ante costs of infection control, that occur whether an infection occurs or not, are largely ignored in much of the work on the economics of infection. Furthermore, there is little agreement about the effectiveness of some preventative procedures that may be carried out in the belief that they will reduce the risk of infection but in the absence of any evidence that they do (Daschner, 1985).

Estimation of the costs of prevention is therefore limited to the costs of key preventative activities. Methar *et al* (1993) provide some estimates of aspects of costs of infection control in the UK. However, lack of clear budgetary responsibility for the control team makes costing difficult. Some of the members of the team share their time between different activities and so apportionment is not easy. Other types of costs are buried in the budgets of pathology or medical microbiology departments. Attempts have been made to itemise costs of the microbiology laboratories including the cost of equipment, consumables and human resources (Bevan, 1995.) However, it is difficult to see how accurate costs can be obtained whilst budgetary arrangements are so entangled unless some painstaking observational studies were undertaken.

What does seem apparent is that less is spent in the UK than in the US on infection control practices. For example, a survey of ICTs carried out in the UK in 1993 found that on average one ICN covers 477 acute and 376 non-acute beds. Almost 20 per cent of the infection control nurses surveyed covered in excess of 750 acute beds, which in some cases were spread over several hospitals, as well as non-acute beds (Cookson, 1995; DH/PHLS, 1995). This compares to the US accreditation requirements of one ICN per 250 acute beds. (Cookson, 1995; DH/PHLS, 1995).



## Management of infection control

It is one thing to set up a system for organising infection control it is quite another to ensure that such an organisation works well; that procedures and protocols are followed; that responsibility and accountability for implementation is clearly set out, audited and monitored.

The multi-dimensional risk factors for infection raise problems in so far as it is difficult to attribute responsibility for failures of policy and practice amongst members of the infection control team and other members of the clinical, scientific, domestic and administrative works within the hospital. There are many pressures upon individuals in addition to their duties with respect to infection control; they have to make judgements about the use of their time, take decisions about the risks of exposure and have little information on which to base such judgements. The choice of rinsing a glass rather than washing it may be of no consequence except on rare occasions when the person last using it had some infection that was easily transmissible; the time taken to wash hands between dealing with different patients may seem a luxury on a busy ward. Only after the event, when it becomes likely that person to person spread of infection has occurred as a result of lack of washing one's hands, does the action appear to have been necessary. The infection control team might educate, monitor and audit but they are not able to directly supervise staff who are accountable to others for their day to day activities. It is difficult to assess benefits given that they depend on risky and uncertain outcomes. Clinicians and nurses are also exposed to risks. It seems, however, that they are no more at risk from the effects of exposure to infection than workers in other industries are at risk from other hazards, (Cohen, 1984). Clinicians infected with viral hepatitis or HIV may, however, in addition to their own problems, pose special problems for those whom they treat. Other infections may affect a staff member to a minor extent but be catastrophic for a vulnerable patient, (e.g., infection involving MRSA), and may then threaten the wider community. The hazards associated with spread of infection can result in doctors and nurses being excluded from patient care either on a temporary basis until they pose no further threat or permanently – involving career changes from clinical care to other duties.

It is recommended that infection control should be written into every contract which purchasing authorities place with units providing services (DH/PHLS, 1995). The way in which infection control is incorporated into contracts is very important. Some

aspects should be spelt out in full in the form of guidelines and protocols. Others are perhaps better treated by general clauses, backed up by an understanding between the contracting parties about what might and might not be regarded as good practice. The element of risk in contracting in the presence of the possibility of infections is difficult to assess. The guidelines for managing infections suggest that all necessary resources should be used to control an outbreak and that financial arrangements should be tackled afterwards. This places provider units in some difficulty if they subsequently cannot achieve a reasonable settlement. Yet purchasers fear that the too liberal acceptance of the burden of the costs of outbreaks might encourage inappropriate future claims.

We explore the economic impact of infection in the next section.

# 7 THE ECONOMIC EVALUATION OF HAI

## Introduction

Resources are scarce: the alternative uses to which they can be put are many. The task for the economist is to indicate the consequences of using resources in one way rather than another. A hospital infection has been described as a 'lose, lose scenario' (Haley *et al*, 1987): patients suffer adverse consequences and health sector resources are used up dealing with a problem that is, to some extent at least, preventable. The questions that arise in connection with economic evaluation of HAI are, 'What does it cost to all those concerned?' and, 'What are the most cost effective methods of intervening to prevent or limit either the impact or the spread of HAI?'

HAI has been the subject of relatively few economic evaluation studies, given the size of the problem, although, like economic evaluations in other fields, these have been increasing sharply since the mid-seventies (Haley, 1992). This lack of material is partly explained by the methodological problems associated with evaluation of HAI and the large and costly samples required to study HAI.

Lack of studies and the paucity of the data available on costs have not deterred researchers from making national estimates of the costs of infection. In 1988 a joint DHSS/PHLS working group estimated that 950,000 bed days were lost at a cost to the NHS of some £111m (DHSS/PHLS, 1988). Recently Coello *et al.* (1993) estimated the costs of HAI occurring in surgical patients in England to be £170m. Haley estimated the costs of HAI in the US to be \$4bn (Haley, 1985c). This estimate was based on the findings of an earlier study which limited the range of costs included to extra days in hospital (Haley *et al*, 1981). This approach, though crude and deficient from an economic point of view, does serve to indicate the extent of the problem and the reasons for enquiring more deeply into the issues.

In this chapter we will survey some of the work that has been undertaken and consider the gaps that remain in our knowledge of the economics of HAI. This review is not intended to be a systematic account of the work conducted in this area but a wide range of material has been examined<sup>1</sup>. It begins by considering the basic

<sup>1</sup> Information was retrieved through (i) Medline searches (ii) cascade referencing key articles (iii) examination of reports and working papers and (iv) discussions with experts in the field.

framework for an economic appraisal of HAI, indicating the methods used to define HAI and to attribute the extra resources used because of infection. Studies of particular infections and the benefits of various preventive procedures will conclude the chapter.

Evaluating infectious disease control consists of evaluating an absence. The avoidance of any infection potentially frees up resources that may be used for other purposes. A bed used by someone suffering unnecessarily from an infection, given the resource constraints confronting the hospital sector, deprives someone else of care: it has an opportunity cost. Evaluations of HAI typically take the form of a cost-of-illness study. These provide minimum estimates of the value to society of the avoidance of disease. Some of the earliest economic evaluative studies were of this type (Fein, 1971) but economists are wary of them because they do not measure benefits as such but potential resources that might become available if the illness no longer existed (Mishan, 1971; Culyer, 1985). Thus cost-of-illness studies do not in themselves provide guidance about the allocation of resources. They do, however, indicate the potential benefits that may arise, in terms of costs avoided, if infections could be eliminated from the system. Furthermore they have been influential in setting the agenda for policy initiatives and for initiating further evaluative studies (Rice, 1995).

## Classification of costs

Because the costs of infections are distributed amongst so many different agents it is important that the widest possible view is adopted when assessing where the costs fall. Infectious disease imposes burdens on those who are not themselves able to influence its prevention or control. Cost-of-illness studies of HAI should attempt to include all the resources used up as a result of the infection: direct costs result from resources being used to treat or control the infection and indirect costs or losses arise as a consequence of the infection to the individuals and organisations involved. Figure 2 illustrates the categories of costs borne by the various institutions and people involved.

## Comprehensiveness of costs included

Estimates of costs of HAI rarely extend beyond the cost to hospitals. Haley (1992) considers that this deficiency is perpetuated by the use of economic studies to persuade hospital managers of the financial



Figure 2 Classification of costs

<b>(I) Health sector costs</b>	
<b>Hospital services</b>	
<b>Inpatient stays</b>	<b>Outpatient consultations</b>
Inpatient days	Consultations
Investigations	Investigations
Treatment	Treatment
<b>Primary care services</b>	
<b>General Practitioner</b>	<b>District Nursing and other services</b>
Consultations	Nursing care
Investigations	Investigations
Treatment	Treatment
<b>(II) Costs to patients and families</b>	
<b>Out of pocket expenditures</b>	<b>Other consequences</b>
Travel	Death
Medicines	Anxiety
Miscellaneous expenses	Pain/discomfort
<b>(III) Other costs to society</b>	
<b>Production losses due to morbidity</b>	

importance of infection. The studies rarely take into account costs to general practice and community services nor the direct and indirect costs to patients and those who care for them. Indeed, hospital costings often rely only on rather crude estimates of the costs of extra length of stay. These may not reflect the resources used up as a result of the infection or the opportunity costs of treating the infected person. Also, studies often fail to place value on the lives lost as a result of infection. The wider impact of infections are rarely discussed. Thus most of the studies underestimate the impact of infection.

This failure to estimate the costs faced by the community care sector is very important especially as lengths of stay in hospital are being reduced. Shorter length of stay may both reduce the exposure to the threat of infection and increase the likelihood of any infection being identified for the first time once the patient has been discharged thus shifting the burden of costs to agencies outside the hospital.

Infection may affect the recovery of patients from their illness, cause distress and anxiety, and extend the time off work of the patients and those who look after them. In addition expenditure on

travelling to hospitals or general practices, on drugs and other items associated with the illness may be incurred by those with a HAI.

Few studies include the impact of infection on other agencies. An exception is a Finnish study that considered the implications for the social security system (Hyryla, 1994). Finally, the economic appraisal of HAI should, if it is to be comprehensive, include the value of lives lost. Within the health sector values are rarely placed on lives lost and as such in the context of HAI it may perversely appear that the acquisition of an infection that results in death is relatively cost free.

## Identifying a case

In order to calculate any costs of HAI it is necessary to have a reliable method of identifying HAIs and attributing additional resource use to it. The identification of an HAI depends upon the definitions applied, the methods used to detect cases and the quality of the surveillance methods used. The data can be collected prospectively or retrospectively with the accuracy of the latter dependent on the quality of record keeping.

## Attribution of resource use to HAI

Attributing resource use to infection is difficult (McGowan, 1982). Issues of attribution are usually focused upon extra hospital days. One of the simplest methods of attribution is by crude weighting: the extra days spent in hospital by patients with an infection are estimated and an average cost applied to each bed day. Haley (1992) criticises these 'back-of-the-envelope' estimates that are often used to 'create political urgency' and to get infection on to the political agenda. Two further methods of attribution that have been used are the concurrent and the comparative.

The concurrent method requires professionally qualified staff to estimate which items of cost can be attributed to infection. Attribution using subjective clinician's judgement is often described as 'direct attribution' (Haley, 1992). Scheckler (1978) used a nurse/epidemiologist to estimate by how much length of stay had been extended as a result of infection. However, McGowan (1982) argued that it would be difficult to tell whether the judgements made would be reproducible from person to person, or whether the judgements of the same person are reproducible in two different time periods. Physicians may also be reticent about attributing extra resource use to the HAI, consequently costs are likely to be underestimated. In a study by Wakefield *et al* (1987), trained

personnel reviewed medical records using a carefully prepared protocol. Each day of a patient's hospital stay was categorised according to whether it was (i) attributable to the reason for admission, (ii) jointly attributable to the reason for admission and the infection, (iii) attributable to the infection alone. Although this approach was considered both repeatable and valid it relied upon good hospital records.

The comparative method compares two groups of patients, infected and non infected. However, if a straight comparison is made it would be difficult to be sure that the additional costs of the infected group are all attributable to the infection. The groups may be different with respect to a number of factors some of which are associated with increased resource use. To overcome this cases and controls should be matched on the basis of key patient characteristics, such as, sex, age, diagnosis, treatment procedures and co-morbidities. The resources used by cases and those chosen as their controls are then compared and the difference used to estimate the differential costs. However, matching is difficult, a very large sample is required and even in large samples only the major factors likely to affect resource use can be included. Haley found that 'The better the matching, the lower the estimate of extra days due to infection' (1991 p355).

Haley, *et al* (1980) suggested the comparative method overestimated the burdens of HAI compared to results obtained from concurrent analysis. This may be because of a failure to adequately control for differences between infected and uninfected patients other than the infection itself (Haley, 1992). Two additional control variables were suggested. One was the time spent in hospital prior to the infections (an attempt to ensure the patients were similar before the infection occurred), and the other was to include diagnosis on discharge as well as on admission. Costs were found to increase with the number of diagnoses up to three diagnoses. Haley considered that this meant that this added parameter was distinguishing a group of simple cases with only one main diagnosis from those with more than one diagnosis. This seems plausible except for those cases in which the existence of the infection may of itself have contributed to the number of diagnoses on discharge. Intent upon obtaining some good indicator for severity Haley (1991) also used Diagnostic Related Groups (DRGs) which he considered were the best way of predicting a patient's length of stay and total hospital costs. He applied DRGs to the large SENIC data base and found that the DRGs explained 30 per cent of the length of stay and 50 per cent of the infections.



An ongoing study of the socio-economic burden of HAI uses a different approach to attributing costs of HAI, (Plowman, 1994). Prospective data on resource use were collected for a cohort of patients and statistical regression techniques were used to model the extent to which the presence of infection, alongside other factors, explained any difference in observed cost. The robustness of the model will depend on the accuracy with which the impact of the various parameters on the use of resources to treat HAI can be estimated. This statistical approach will provide confidence limits for the estimates.

Regardless of the method used to attribute costs, the sensitivity of study results to changes in key assumptions should be assessed. For example, if LOS was thought to be extended by 7 days as a result of a SWI, what would the impact be on total costs if this figure was changed to 6 or 8 days? The use of this type of analysis helps researchers to ascertain which assumptions have the greatest influence on the results of the study. Sensitivity analysis is not, however, commonly used in the literature measuring the impact of HAI.

## Costs of resources used to treat or control HAI

Once issues of resource attribution have been sorted out costs have to be estimated for the resources used. Economists measure costs as the benefit forgone by using resources in one way rather than in another, more precisely the next best alternative use. In the case of HAI it is likely that resources absorbed to care for those infected would, in the absence of the HAI, have had alternative uses. The forgone benefits of these represent the opportunity costs of HAI.

Many studies depart from this requirement because they focus upon the average costs of an extra day spent in hospital. Both the traditional cost accounting conventions adopted in the NHS and the price/charge ratios used in the US health care sector may distort the measured cost of resources (Cooper *et al*, 1987; Haley, 1992). Dawson (1994) argues that costs derived from the UK health sector are usually the result of mechanistic accounting conventions designed to recover expenditure rather than reflect resource use. For example, the allocation of overheads and capital charges are made by convention. These costs are a significant proportion of total cost (Magee *et al*, 1978; Seawell, 1984). The use of charges in US hospitals may introduce further distortions because 'to maintain financial balance, hospitals tend to shift their charges for under-reimbursed costs to those [payers] with which they can recover more than their



costs' (Haley, 1992 p522). To overcome this some studies have applied a cost-to-charge ratio. This has been estimated as between 0.6-0.8 depending on the hospital and unit concerned (Haley, 1991).

In addition to the above problems in-patient stay is decreasing sharply and comparisons over time which focus on the cost of extra days in hospital may not be reliable. Indeed, average additional length of stay associated with HAI may be falling. This reduction does not mean that costs of HAI have necessarily fallen. Some of the costs may have been shifted to the community: to individuals, general practice, community services and residential homes.

A further problem with the use of average unit costs is that average costs are a function of the total quantity produced (in this case, of hospital inpatient days). Average costs estimated from hospitals operating at different levels of capacity will therefore differ. Daily costs also vary over the hospital stay. They tend to be high for the first day or so after admission and then fall sharply (Hollingsworth *et al*, 1993). In the case of HAI it is likely that for some infections the costs would have a second peak around the time that the HAI presented. Average cost per bed day may not reflect the resources used to treat a patient with an HAI, who may cost more or less than the average for all patients (both with and without HAI), depending on the type and severity of the infection. Clearly a better measure is required if we are to assess the potential impact of infection and the potential savings that might accrue from prevention. A more appropriate measure would be the marginal cost of HAI, 'what is avoided (and saved) if a patient is prevented from getting an infectious complication' (Haley, 1991 p335).

We will now consider studies that can be broadly classified as using a cost-of-illness framework and then consider studies that have directly addressed the cost-effectiveness of prevention.

## Review of cost-of-illness studies

In addition to individual studies that estimate the costs of HAI, there are several articles that review the material. Review articles by Haley (1992), Smith *et al* (1996) and Currie *et al* (1989) are particularly useful. Haley's work, undertaken in connection with the original SENIC study, and subsequent studies that have used this as a data base and refined methods of analysis are of great importance.

A pattern emerges from the studies that indicates that a few infections account for a large proportion of the cost to hospitals. Infections of the lower respiratory tract, thought to represent about 14 per cent of all infections in the US, accounted for 29 per cent of the

estimated costs of HAI. SWIs absorbed half of the expenditure on infection although they represented only 25 per cent of the infections recorded. SWIs after injury have been found to be particularly expensive (Pinner *et al*, 1982).

HAIs frequently present after discharge from hospital. Holtz (1992) in a review of the literature found that up to 70 per cent of SWIs do not present until after discharge. These infections inevitably will have implications for the primary health care services' resource use (Elliston *et al*, 1994) and for the individual and those who care for them.

When considering individual infections the least costly tend to be the UTI's, while the more costly infections tend to be those of the bloodstream, multiple sites and pneumonia. A US study estimated the costs of UTI to be \$594, SWI \$2,734, pneumonia \$4,947 and blood stream infection \$3,061 (Haley, 1986). Pittet *et al* (1994) estimated that bloodstream infections imposed extra costs per survivor of \$40,000.

An outbreak of MRSA can be very expensive. Costs may include ward closures, cancellations of operations and admissions and cause staff to be tested and excluded from work. For example, an outbreak which lasted 2 years was found to cost £403,600 (Cox *et al.*, 1995). The earning capacity of the hospital may be reduced, reputations affected and the burden in excess morbidity to patients high.

The findings from some of the major studies are shown in Table 4.

The most recent study conducted in the UK involved 67 surgical patients with an HAI. These patients were matched with controls on the basis of age, sex, surgical specialty, diagnosis and first operative procedure. Differences in resource use by infected and uninfected patients were estimated in terms of duration of hospital stay, antibiotic treatment administered and the number of microbiology, haematology, chemical pathology and radiology tests. Cost estimates were then applied to these data variables. It was found that orthopaedic patients incurred the highest costs (£2,646) and gynaecology patients the lowest (£404); multiple infections were found to cost £3,362; while SWIs cost £1,454 and UTIs cost £467. No attempt was made to estimate the impact of HAI on primary health care and community services, the individual concerned or those who care for them.

An outbreak of infection involving multiple-resistant *Salmonella heidelberg*, affecting 17 patients and 2 staff, was comprehensively costed by Barnass *et al* (1989). The direct costs of the outbreak were estimated at £21,151, 85 per cent of which was borne by the hospital with 17 per cent attributed to the microbiology department. The opportunity costs of ward closures were not included but allowance

**Table 4 Results of cost-of-illness studies of HAI by type of infection, length of stay and extra costs or charges 1978-1994**

Site of HAI	First author and date of publication	Type of patients studied	Number of infections	Country	Results	
					Extra days in hospital	†Extra cost/charges per case
UTI	Coello (1993)	General surgery, orthopaedic and gynaceology	36	UK	3.6	£498
	Haley (1981)	All admissions	177	US	1	£891
	Rubenstein (1982)	General surgery and orthopaedics	30	US	5.1	£653
	Scheckler (1978)	All admissions	38	US	0.6	£312
SWI	Davies (1979)	Orthopaedic	29	UK	17.0	£1,741
	Rubenstein (1982)	General surgery and orthopaedics	19	US	12.9	£1,652
	Mugford (1989)	Caesarean section	41	UK	2.1	£1,011
	Coello (1993)	General surgery, orthopaedic and gynaecology	12	UK	10.2	£1,553
	Poulsen (1994)	Surgical patients	291	Denmark	5.7	no data
	Scheckler (1978)	All admissions	16*	US	7.5	£2,937
	Sheckler (1978)	All admissions	10*	US	3.7	£1,612
Pneumonia	Kappstein (1992)	Intensive Care Unit	34	Germany	10.13 (ICU days)	£5,533
	Rubenstein (1982)	General surgery and orthopaedics	8	US	18.0	£2,305
Multiple	Coello (1993)	General surgery, orthopaedic and gynaecology	9	UK	26.2	£3,588
	Freeman (1979)	All admissions	27	US	8.7	no data
LRTI	Haley (1981)	All admissions	75	US	6.0	£7,436
	Haley (1981)	All admissions	8	US	7	£4,601
Blood-stream	Pittet (1994)	Surgical intensive care	86	US	14	£22,489
	Girard (1983)	Neonates	61	France	6.7	£1,118

Source: Compiled from studies separately referenced.

Key: SWI, surgical wound infections; UTI, urinary tract infections; LRTI, lower respiratory tract infections.

\*All costs have been converted into sterling using the OECD 'Health Data' database (1996). They have been adjusted to 1995/96 prices by using a factor series that takes account of hospital input cost inflation in the UK (DoH 1997).

\*Patients in this study may have more than one infection.



was made for those not able to work until they were free from infection. Antibiotic therapy is not normally given for *Salmonella* but in this outbreak oral ciprofloxacin was administered to prevent infection of a joint prosthesis; to eliminate infection in the immunocompromised; to enable urgent surgery to be carried out and for the treatment of septicaemia. Costs of extra nursing and medical supplies were itemised. It is a rare study in that it documents the opportunity costs associated with investigations, meetings and visits relating to the control of the outbreak.

There are a small number of papers that consider a wider range of costs. In the US, Rutledge *et al* (1985) estimated one million hospital patients acquire a urinary tract infection generating extra hospital charges of \$1.8 billion as well as giving rise to 'hidden costs' such as lost earnings and other social burdens due to disability and death. Persson *et al* (1988) included a value for the loss of health suffered by patients as a result of infection.

In a prospective study of 1,458 patients with in-dwelling urinary catheters 136 UTIs were observed and 76 patients died during hospitalisation; death rates were 19 per cent in infected patients and 4 per cent in non-infected patients (Platt *et al*, 1982). The acquisition of infection was not associated with the severity of underlying disease; among patients who died, infections occurred in 38 per cent of those classified as having non-fatal underlying disease and in 27 per cent of those classified as having fatal disease. The authors concluded that the UTI in patients with in-dwelling urinary catheterisation was associated with a threefold increase in mortality among hospitalised patients.

As indicated earlier, data from the US suggest that 10 per cent of patients with an HAI die in hospital. In 10 per cent of these deaths the HAI was the main cause and in another 30 per cent HAI was a contributing factor. If these percentages are applied to the US population, then 20,000 deaths in the US may be directly attributable to infection each year and in a further 60,000 deaths HAI may be a substantial contributor (Haley, 1986).

As discussed earlier, it is important that a value is applied to these lives lost. However, valuing lives lost presents a number of difficulties: what value should be applied to each life lost and what was the relationship between the HAI and death? The Department of Transport suggests a value per life lost in road accidents of £841,000 (Highways Economic Note Number 1, August 1996). If, for illustrative purposes, this is applied to the 20,000 deaths estimated to be the direct result of an HAI in the US, then the value of these deaths is estimated to be £17billion. In the UK it has been estimated that 5,000 deaths are directly attributable to an HAI (DH/PHLS,



1995). If the same value is placed on these lives lost then the estimated additional burden amounts to £4.2billion.

## Cost-effectiveness of prevention

This section addresses the second question posed at the beginning of this chapter, 'What are the most cost effective methods of intervening to prevent or limit either the impact or the spread of HAI?'

Whilst the cost-of-illness studies provide interesting information about the extent of the burden of HAI perhaps the greatest contribution of such studies is in pointing to the need to develop intervention strategies. First we will describe some studies of the cost-effectiveness, or otherwise, of specific preventive interventions. We then conclude with a discussion of evaluations of general measures to control infection, and the incentives that might encourage managers to adopt control programmes.

Perhaps one of the most significant interventions with respect to prevention of HAI revolves around the use of prophylactic antibiotics. This is expensive and to be worthwhile it needs to be effective both in the short term control of infection and in the longer term, minimising the possibility of accelerating resistance to antibiotics. The costs and benefits of peri-operative antimicrobial prophylaxis have been addressed in a review article by McGowan (1991). According to a survey carried out in the US in the 1970s, about one third of all anti-microbial use was for peri-operative antimicrobial prophylaxis (Shapiro *et al*, 1979). Using data from a placebo controlled trial of cefazolin sodium prophylaxis in women undergoing either an abdominal or vaginal hysterectomy, Shapiro *et al* (1983) found that the use of this anti-microbial reduced costs by \$102 and \$492 per patient respectively. These savings would have been lost, however, if newer, more expensive cephalosporins had been used (unless they were more effective) or if the duration of prophylaxis had been extended. In caesarean section (Jones *et al*, 1984), colon resection (Hojer, 1978) and vascular surgery (Kaiser *et al*, 1983) it was found that peri-operative anti-microbial prophylaxis was more cost-effective than treating the infections that might have otherwise occurred.

The National Perinatal Epidemiology Unit in Oxford undertook a meta-analysis of randomised controlled trials of antibiotic prophylaxis administered to patients undergoing caesarean section (Mugford *et al*, 1989). The analysis included 16,000 patients. Wound infections were defined as either a positive culture or pus in the

wound. The mean incidence of SWI in the groups not receiving prophylaxis was 9 per cent whilst for other post-operative infections it was between 26-40 per cent. Some of these were serious infections, such as pelvic abscess and septicaemia. The HAI infection rate in patients receiving antibiotics was about one third of those in the untreated group. It was not possible from this analysis to identify the mothers most likely to benefit from the prophylaxis. The group concluded that prophylactic antibiotics at the time of the caesarean section is cost effective. The expenditure on antibiotics was more than compensated for by savings that accrued from reductions in in-patient stay and therapeutic antibiotics, although such findings were thought to need assessing more fully in a controlled trial (Howie *et al*, 1990). A Swedish study explored the cost-effectiveness of alternative regimes for prophylaxis in orthopaedic surgery (Persson *et al*, 1988). In general, the more expensive the prophylactic regimen, the lower was the incidence of deep sepsis and the subsequent re-operation rate, and the cost-effectiveness of a particular regimen was dependent on the number of arthroplasties performed.

It does not appear that prophylaxis is useful in all operations (e.g. gallbladder surgery) and not all peri-operative regimens are effective (McGowan, 1991). A survey of community hospitals in Florida identified that in those cases where prophylaxis was thought to be justified, 32 per cent of regimens had inadequate dosages; 24 per cent of regimens were begun too late (i.e. post-operatively); and in a further 23 per cent of cases drugs were continued for too long. It was estimated that \$36 was wasted per operation; \$9 due to using unnecessarily expensive drugs and \$26 due to inappropriate use (Fiore *et al*, 1984). Davey *et al* (1995a) compared the cost-effectiveness of prophylactic administration of amoxicillin/clavulanic acid (augmentin) in patients undergoing abdominal and gynaecological surgery, with other antibiotic regimens, using data from 21 previously published trials. Amoxicillin/clavulanic acid was found to be less expensive than 19 of the comparators and equally or more cost-effective relative to a wide range of comparator regimens.

McGowan argues 'The least expensive drug with adequate therapeutic efficacy should be used for the briefest effective period,' (1991 p887). This being so, the key seems to be education of clinicians in the appropriate antibiotic regimens. To this end, computer generated messages or reminders about peri-operative care placed in patients medical notes before surgery have been found to reduce wound infections by half. Education was also seen to be important in discouraging inappropriate use. A study in the US

indicated that in 53 per cent of cases where antibiotics were prescribed there was no apparent indication (Smith *et al.*, 1988). This in turn may lead to considerable costs savings. Expenditure on practices which have little or no beneficial effect, or which have a cheaper yet equally efficacious alternative clearly represent a waste of scarce resources.

Daschner has examined the rationale and the costs of many practices thought to reduce the risk of infection. He concludes that many have no proven efficacy or that cheaper alternatives exist. Consequently he has advocated discarding the use of a range of consumables in wards and theatres thereby leading to substantial cost savings in hospitals. For example, he advocates the replacement of disposable plastic vacuum bottles for wound drainage with reusable glass bottles, a change that has led to considerable cost savings in the department where he works (Daschner, 1985; 1991). Lynch *et al.* (1992), in a double blind, placebo-controlled randomised trial, examined the efficacy of pre-operative 4 per cent chlorhexidine body washes and found that, although this led to a significant reduction in bacteria on the skin, this was not associated with any statistical significant reduction in wound infections. Expenditure on pre-operative chlorhexidine body washes therefore represented an unnecessary drain on resources (Lynch *et al.*, 1992).

**Table 5 Yearly costs and benefits of an infection control programme in an average 250 bed hospital in the US assuming 3 possible levels of programme efficacy – 1985 US dollars**

	Assumed reduction in hospital acquired infections		
	6%	32%	50%
Number of patients prevented from having an infection	42	168	262
Number of extra hospital days avoided by reduced infections	160	640	1,000
Hospital dollar costs avoided by reduced infections	\$60,000	£320,000	\$500,000
Costs of the infection control programme	\$60,000	\$60,000	\$60,000
Net savings to the hospital	\$0	\$260,000	\$440,000

Source: Haley, 1986



## Incentives for prevention

As long as providers do not receive financial compensation for treating the consequences of HAI 'a strong financial incentive will exist to establish and maintain prevention programmes that will effectively reduce infectious complications and the attendant prolongation of stay and extra ancillary costs' (Haley *et al*, 1987 p1611). It is however necessary to demonstrate that the infection control programmes are effective. Haley *et al* (1987) consider that by focusing preventive techniques on 'specific, measurable prevention objectives' control programmes will produce measurable reductions in HAI. Estimates have been made of the savings derived from the introduction of an infection control programme. For example data from the SENIC study suggested that as much as 32 per cent of infections might have been prevented if there had been effective infection control programmes. Essential components of effective programmes included organised surveillance and control activities; the employment of a trained infection control physician; one infection control nurse per 250 beds; and a system of reporting infection rates back to surgeons. The cost of such programmes in 1985 was estimate to be \$60,000 for every 250 bed hospital. Consequently a 6 per cent reduction in infections would pay for the infection control programme and greater reductions would result in greater returns. Haley *et al* also identified diminishing returns to the identification of infections. It was noted that 75 per cent of the infections could be detected in the first 20 hours and nearly all of the remaining can be detected in the next 20 hours (Eickoff, 1981).

In the UK it has been estimated that a reduction in incidence of HAI by 20 per cent, 32 per cent and 50 per cent would produce annual savings of £15.6 million, £29.3 million and £50 million pounds respectively to the NHS after offsetting the costs of the infection control teams and their programmes (Currie *et al.*, 1989). However, this work is largely suggestive and descriptive rather than evaluative and more research is necessary in this area.

It is important, for policy purposes, to understand the financial incentives for reducing infection. Wenzel (1985, 1987) considered the impact of diagnostic related group (DRG) related reimbursements in the US and concludes that although some allowance is made for HAI in the standard charge, payments appear to force the hospitals to bear the costs of HAI. By re-examining SENIC data and classifying each admission into a baseline DRG after first excluding all diagnoses of HAI, and then comparing this with the final DRG, it was found that only 5-18 per cent HAIs would have caused a



reclassification to a higher-paying DRG. In those cases an extra payment of \$93 per infection would have been made, representing only 5 per cent of the estimated hospital costs of treating these infections.

Incentives for infection control in the present UK contractual system will depend upon the contractual arrangements. Clauses about control of infection are included in most contracts for in-patient care but they are very general and rarely monitored. A recent audit of infection control activity in 19 district general hospitals in England and Wales (Glynn, 1997), found that 10 purchasers had asked for the surveillance of HAI. Of these, six requested that rates were calculated, and two of these wished to see the rates. Two purchasing authorities did not ask for surveillance of HAI but were however interested in HAI rates. Of the remaining seven purchasers, six did not request either surveillance or rates. Information was not available on the remaining purchaser. It is not clear what priority Trust hospital managers give to infection control or whether they are aware of financial implications of infection for hospitals or the possible effectiveness of an infection control programme. More work in this area is clearly required.

Although many of the evaluative studies are methodologically imperfect the patterns that emerge are credible and consistent. There is much work that needs to be done to evaluate interventions to reduce HAI and to develop incentive structures to facilitate the development of appropriate control policies.

## 8 CONCLUSION

At any one time, approximately ten per cent of hospitalised patients, equivalent to several hundred thousand people every year in the UK, have a HAI. These infections cause additional morbidity and impose substantial financial burdens on the hospital and community health care services, patients and those who care for them.

Many studies have estimated the costs incurred as a result of these infections some of which have been discussed in this paper. As noted, the studies vary in terms of the types of infections and patients studied, the range of costs included, and the methods used to estimate the cost of resources used and to attribute costs to the infection.

Despite methodological differences, the findings of these studies clearly demonstrate that HAI is a significant burden to the hospital sector. A consistent pattern emerges: some relatively rare infections, together with multiple infections, have very high costs per case but the more common infections such as SWIs and UTIs represent the biggest strain upon hospital resources.

Little is known about the resources used to care for those affected by HAI once they return to the community. Since costs falling on the primary health care and community care sector are likely to increase in the future, it is of increasing importance that these costs are included in any evaluation of the cost of HAI. Inpatient stays are shrinking, with patients being discharged into the community at an earlier point in their recovery and as such it is likely that there will be a shift of resource use from the secondary to the primary health care sector. Furthermore, although a reduced hospital stay will inevitably reduce the risk of acquiring an infection, it is not clear by how much and it is likely that there will be an increase in the number of HAIs presenting post-discharge, which in turn will have implications for resource use and costs.

HAI also has a cost impact on patients and those who look after them. For example, HAI may result in an increase in personal expenditure and disruption to work or leisure patterns. Few studies have attempted to quantify these costs.

The impact of HAI on morbidity and mortality is another area often neglected in these studies. However, it is clear that HAI prolongs the recovery period, in some cases is the primary cause of death and in others it is a substantial contributor to death. It has been estimated that 5,000 deaths per year in the UK are a direct result of

HAI and in a further 15,000 deaths HAI is a significant contributing factor. This makes HAI a more common primary cause of death in the UK than either road traffic accidents or suicide. If a value is placed on lives lost the extent and importance of the problem is brought into sharper focus. It is then possible to compare the investment programme on infection control with life saving programmes in other sectors, such as transport safety.

Turning to the costs of prevention, data from the US have demonstrated the importance and the potential cost-effectiveness of a well designed prevention and control program. It has been estimated that preventative programmes which include the appropriate personnel and, importantly, surveillance of infection with feedback of the results to those who need to know, have the potential to reduce infection rates by a third. It is believed that similar reductions could be achieved in the UK.

Giving up practices and procedures that have been demonstrated to be ineffective will be an important part of a cost-effective prevention programme, as will the more considered and selective use of antibiotics. The latter is important not only in preventing infection but also in containing the emergence of resistant organisms. So far, the development of new antibiotics has kept slightly ahead of the ability of most organisms to adapt and acquire resistance. However, the emergence of MRSA, multi-drug resistant *Mycobacterium tuberculosis* and other resistant organisms indicates that this may not always be the case. Policies relating to the use of antibiotics should be co-ordinated on a national level and in some cases at international level to prevent the emergence of resistant organisms.

The current level of investment in infection control in the UK is unclear. The costs associated with infection control are not restricted to the costs of infection control teams. Infection control activities are integrated into all aspects of health care practice and as such it is almost impossible to derive a comprehensive estimate of the investment in infection control. However, it is interesting to note that the level of investment in designated infection control nurses in the UK is considerably lower than in the US. In the US, hospital accreditation regulations stipulate that there should be one ICN per 250 acute beds. In the UK a recent survey found that on average there was one ICN per 477 acute beds with some ICNs covering up to 750 acute beds in addition to non-acute beds.

Methods and approaches of economic appraisal have an important role to play in determining the level of investment in infection control, the development of cost-effective preventive



programmes and in ensuring that appropriate incentives are in place. More value can be extracted from evaluative studies by conducting systematic reviews of the literature concerning infection (Egger, 1993); meta analysis (Cochrane Centre, 1995) and economic modelling. The latter provides a method that allows the impact of infection rates and interventions to be explored interactively using different rates or costing profiles.

The information generated by such studies may usefully be utilised by planners and managers of health care to enable them to address the issues relating to HAI when contracting for care. It is recommended that all contracts include clauses relating to infection control. However, not all contracts currently have such clauses, and those that do are often difficult to operationalise or monitor. The new contractual arrangements place budgetary pressures on units treating patients with HAI which may not be adequately covered by contracts. The private sector also finds infections difficult to finance. Residential homes are increasingly finding it difficult to insure against outbreaks of infection. The sharing of financial risks associated with infection has not been adequately addressed in the literature on managed markets in reformed health services.

Finally, until now demands for infection control have largely been driven by health care professionals: nurses, doctors, microbiologists and specialists in public health. Increasing consumer involvement in health care, in particular the increased emphasis on providing information to patients about the quality of hospitals and empowering them to make choices, may add a further pressure group lobbying for investment in measures to reduce HAI. A knowledge and appreciation of the costs involved is likely to raise the profile of HAI in the minds of managers of health services, possibly resulting in their being more receptive to these demands and themselves actively seeking to improve infection control.



## GLOSSARY

*Aetiology* – cause of disease

*Allocative efficiency* – the selection of the optimum combination of goods produced

*Appraisal* – the process of defining objectives, considering alternatives and considering the costs and consequences of available alternatives

*Average cost* – the total cost of producing a given output divided by the number of units

*Barrier Nursing* – special procedures that aim to prevent the transmission of micro-organisms from an infectious patient to other patients or staff

*Cost-benefit analysis* – a technique which attempts to measure the social costs and social benefits of investment projects to help decide whether or not the project should be undertaken

*Cost-effectiveness analysis* – a technique which compares the methods of producing a given output

*Immunocompetent* – an individual with an intact immune system

*Immunocompromised* – a temporary or permanent state whereby an individual is rendered more susceptible to infection due to an impaired immune response

*Marginal cost* – The change in total cost which results when output is varied by one unit or the avoidable cost of producing an additional unit of output

*Micro organism* – An organism too small to be seen with the naked eye or only just visible. The term includes bacteria, fungi, protozoa, viruses and some of the algae

*MRSA (Methicillin Resistant Staphylococcus Aureus)* – a strain of *Staphylococcus Aureus* that is resistant to many antibiotics

*Opportunity cost* – the value of a resource in its next best alternative use

*Prophylactic* – treatment which aims to prevent disease

*QALY (Quality Adjusted Life Year)* – a measure that combines both the length of life with an estimate of the quality of the life

*Regression analysis* – a set of statistical techniques the purpose of which is to quantify the relationship between two or more variables

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