Chapter 16

The Real Cost of MRSA

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1. INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become endemic in UK hospitals over the last decade. It is primarily responsible for infections of wounds, chest, and urinary tract, but also causes more serious conditions such as osteomyelitis, endocarditis, and septicaemia. Patients usually acquire the organism in hospitals and then return home with it, thus contributing towards the increasing reservoir in the community. The number of serious MRSA infections has increased over the last few years so that over 40% of all staphylococcal bacteraemias in the United Kingdom are now due to MRSA (EARSS Annual Report, 2002). This constitutes one of the highest rates of MRSA infection in Europe.

Eradication of the carrier state is difficult due to the unusually high epidemicity of circulating strains. The prevalent strains in the United Kingdom at present are EMRSA-15 and EMRSA-16, with EMRSA-17 recently described (Aucken *et al*., 2002). These strains are able to adhere to skin, wounds, and mucous membranes, spread between persons, and displace previously resident strains. The complex epidemiology of staphylococci makes any clearance strategy unattractive, especially when the organism has spread widely through an institution to achieve endemic status. Equally difficult is the treatment of MRSA infections, because there are so few effective antibiotics remaining. Those agents, which are clinically effective, tend to be toxic and/or expensive. The overall management of patients with MRSA is therefore perceived as

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time-consuming, costly, and liable to fail. These difficulties have prompted comments in the literature such as, "Trying to control MRSA causes more problems than it solves," "MRSA is a suitable case for inactivity," and even that, "Is it time to stop searching for MRSA? Stop the ritual of tracing colonised people" (Barrett *et al*., 1998; Lacey, 1987; Teare and Barrett, 1997).

Tempting though it is to abandon search and destroy policies for MRSA, there are reasons why continued activity towards control is still strongly recommended. MRSA carriage is more likely than methicillin-susceptible *S. aureus* (MSSA) to lead to infection and MRSA bacteraemia has a worse outcome than MSSA bacteraemia (Muder *et al*., 1991; Romero-Vivas *et al*., 1995). The mortality rate attributed to MSSA bacteraemia in critically ill patients was 1.3% in one study, compared to 23.4% for MRSA bacteraemia (Blot *et al*., 2002). Clinicians may be unconcerned about the possibility that methicillin resistance will become the norm for *S. aureus*, but the very nature of evolution decrees further resistance—notably to glycopeptides (Linares, 2001). It has already been established that patients with glycopeptide-intermediate *S. aureus* (GISA) tend to have an even less favourable outcome than patients with MRSA (Walsh and Howe, 2002).

Such therapeutic difficulties have major implications for the cost of healthcare. A patient found to have infection due to MSSA is usually quickly and easily treated with isoxazolyl penicillins or macrolides. These drugs are relatively nontoxic and cheap and patients can be discharged on oral therapy. Contracting MRSA, however, leads to lengthened hospital stay, prolonged treatment, use of expensive drugs, laboratory costs, and occasionally surgical intervention. Furthermore, successful eradication is not guaranteed, as MRSA can persist for years (Sanford *et al*., 1994). Hospitals with rising numbers of MRSA patients are experiencing an increasing financial burden, which is now impacting upon health policies and overall societal costs. There are also indefinable costs to human health and well being. This chapter will review the evidence for the costs of MRSA within different healthcare systems, the breakdown of these costs and the potential impact of various control strategies on health service resources.

2. COST OF HOSPITAL-ACQUIRED INFECTION

There has already been much interest in the excess costs generated by hospital-acquired infection (HAI). The last few years have witnessed an explosion of reports examining the economic impact of these infections and the most significant contributory factors (Emmerson *et al*., 1996; Haley *et al*., 1981; Jarvis, 1996; Plowman *et al*., 2001). Infected patients, on average, incurred hospital costs that were almost three times higher than those of uninfected patients and they remained in hospital 2.5 times longer (Plowman *et al*., 2001).

It is generally agreed that HAI costs money, which could have been saved if preventative measures had been in place, but there is uncertainty surrounding the most effective control strategies and the best methods by which to measure them (Haley, 1991). Most calculations are based upon the increase in bed-days attributed to HAI (Coello *et al*., 1993; Pena *et al*., 1996) but this methodology has to make assumptions and extrapolations from data not always generated for the purposes of measuring HAI (Walker, 2002). More recent studies provide information on the distribution of additional costs incurred between different hospital sectors or dependent upon patient diagnoses (Zoutman *et al*., 1998). The former includes specific wards such as Intensive Care and Special Care Baby Units, and the latter, conditions such as hospital-acquired bacteraemia, surgical site infection, urinary tract infection, and pneumonia (Hollenbeak *et al*., 2000; Jarvis, 1996; Khan and Celik, 2001; Mahieu *et al*., 2001; Pittet *et al*., 1994; Plowman *et al*., 2001; Rose *et al*., 1977; Spengler and Greenough, 1978).

Some HAI's cost more than others—combined analysis reveals two groups that appear to generate higher costs than for other HAI types; in particular, surgical patients who acquire wound infections and medical patients with lower respiratory tract infections (Lynch *et al*., 1992; Pinner *et al*., 1982). There have been attempts at economic analyses of surgical wound infections (Fry, 2002; Poulsen *et al*., 1994; Reilly *et al*., 2001a). Many studies measure only hospital costs, to varying degrees, and fail to include the costs for community services, follow-up, and social security benefits (Noel *et al*., 1997; Poulsen *et al*., 1994; Reilly *et al*., 2001a). There is little on the direct cost to the patient, in terms of pain, disability, reduction in quality of life, and lost work (Davey and Nathwani, 1998; Poulsen and Gottschau, 1997; Reilly *et al*., 2001a; Whitehouse *et al*., 2002). It is known that HAI may only present when the patient has gone home (Reid *et al*., 2002; Reimer *et al*., 1987; Stockley *et al*., 2001) but the potential savings generated from early discharge may well be negated by the subsequent impact of HAI on patients in the community (Jönsson and Lindgren, 1980; Whitehouse *et al*., 2002).

In the wake of such a drain on healthcare resources, results of various infection control programmes demonstrating cost benefits for both patients and hospital budgets have been presented (Miller *et al*., 1989). There is evidence that surveillance alone will reduce HAI and associated costs (Haley *et al*., 1985; Olson *et al*., 1984), particularly if the results are then fed back to the clinicians involved (Smyth and Emmerson, 2000). Surveillance initiatives should not ignore infected patients presenting post-discharge; for this, the employment of a full-time audit nurse is more than justified in terms of cost-effectiveness (Reilly *et al*., 2001b). There are also significant cost benefits from treating infected patients in their own homes, using outpatient parenteral antibiotic therapy and support staff (Nathwani, 2001).

Comprehensive infection control programmes pay for themselves and more (Haley *et al*., 1985; Miller *et al*., 1989; Wenzel, 1995). There will, however, continue to be uncertainties over the best methods of audit, surveillance, and feedback, which types of HAI require specific attention and which specialities and/or clinical units are most likely to generate the greatest cost benefits for both patients and budgets (Fry, 2002; Haley, 1991). Decisions on where to place control precautions should rest with Infection Control committees in hospital and community, but all require full managerial support (Brachman and Haley, 1981). As with the introduction of any clinical improvement programme, resources must first be released before implementation (Jarvis, 1996; Miller *et al*., 1989).

3. THE COST OF ANTIMICROBIAL RESISTANCE

While the cost of HAI can be aptly demonstrated in the literature, evidence for the cost of antimicrobial resistance is not quite so robust (Coast *et al*., 1996). This is despite the fact that an increasing proportion of HAI is due to resistant organisms (Edmond *et al*., 1999; Schaberg *et al*., 1991). Hospitals seek to provide guidance for the use of antibiotics, but an empirical regimen without targeted cover, or dosed too low to provide optimal therapy, will not eradicate a pathogen. It will also encourage the development of resistance, which then increases patient morbidity and mortality (Paladino *et al*., 2002). Concomitant higher rates of treatment failure and the need for an increase in either the number or duration of hospital admissions will almost certainly be associated with a huge economic burden (Paladino *et al*., 2002; Singer *et al*., 2003).

Infections with resistant pathogens lengthen the stay in hospital, likely to be one of the most significant contributors towards the economic consequences of resistant bacteria (Brooklyn Antibiotic Resistance Task Force, 2002; Kollef and Fraser, 2001; Nathwani, 2003). Managerial costs are increased when infection involves these organisms, as well as unnecessary and prolonged therapy (Niederman, 2001a). Treatment of resistant bacteria is associated with increased drug costs, as the newer, broad spectrum and often far more potent drugs are usually far more expensive than the narrower spectrum agents employed for less-resistant pathogens (Janknegt, 1997). These powerful drugs bring their own particular adverse effects, including the problems generated by overgrowth or superinfection of naturally resistant organisms (Drew *et al*., 2000; Khare and Keady, 2003; Sanyal and Mokaddas, 1999). Other factors to consider are the prohibitive costs required to develop new antimicrobial agents, and the implementation of broader infection control and public health interventions aimed at curbing the spread of resistant pathogens (Kollef and Fraser, 2001).

The economic evaluation of HAI due to resistant organisms is often confounded by the same risk factors that are associated with poor outcomes (Holmberg *et al*., 1987). Resistance is an important risk factor for inadequate empirical therapy. Such therapy is itself a potent determinant of a number of adverse outcomes, including mortality (Niederman, 2001b). Another practical difficulty in actually measuring the economic impact of resistance is the identification of a suitable control population (Coast *et al*., 2002; Niederman, 2001b). Nevertheless, for both HAI and community-acquired infections, the mortality, the likelihood of hospitalisation, and the length of hospital stay is usually at least twice as great for patients infected with drug-resistant strains as for those infected with drug-susceptible strains of the same bacteria (Holmberg *et al*., 1987). The likely cost per capita of healthcare-associated *S. aureus* infection in Denmark and the Netherlands is lower than that in the United States, because MRSA infections, which are rare in both of these countries, cost significantly more than do MSSA infections (Farr and Jarvis, 2002; Farr *et al*., 2001; Janknegt, 1997). A Danish patient with healthcare-associated *S. aureus* would be treated with an old-fashioned β-lactam antibiotic with faster response, higher cure rate, and quicker hospital discharge at lower overall cost to society (Farr and Jarvis, 2002).

Although the adverse, economic, and health effects of drug-resistant bacterial infections can only be roughly quantified, it is concluded that antimicrobial resistance is an important health problem and an economic burden to society (Holmberg *et al*., 1987). Future evaluation of interventions aiming to contain resistance might benefit from the use of modelling as a means of measuring optimal policy response, as well as trying to resolve some of the difficulties associated with such interventions (Coast *et al*., 1996, 2002).

4. GENERAL COSTS OF MRSA

Most authorities would agree that MRSA is probably the most important resistant bacterium associated with HAI. Staphylococci themselves are the most common pathogens causing bacteraemia according to national surveillance of bloodstream infections (Pfaller *et al*., 1998). Along with *Escherichia coli*, they account for over 55% of all bacteraemias from one recent study (Diekema *et al*., 2000). The only major change from similar previous studies was the increase in methicillin (oxacillin) resistance in both coagulase negative staphylococci and *S. aureus* (Diekema *et al*., 2000; Pfaller *et al*., 1998; Schaberg *et al*., 1991). *S. aureus* was the most common pathogen referred to the SENTRY Antimicrobial Surveillance Program from 1997 to 1999, where it was found to be the most prevalent bloodstream infection, skin and soft tissue infection, and cause of pneumonia in all geographic areas studied (Diekema *et al*.,

2001). Similar increases in methicillin resistance were also observed in these isolates, originating from both hospital and community (Diekema *et al*., 2001).

MRSA does not appear to replace MSSA in the overall burden of infection, as the attack rate of methicillin-susceptible strains has not decreased (Stamm *et al*., 1993). MRSA has simply added to the infection rate, particularly the HAI rate (Herwaldt, 1999; Law and Gill, 1988; Stamm *et al*., 1993). At some point in the future, when the prevalence of MRSA is such that *S. aureus* can be redefined as "naturally" methicillin resistant, MRSA will replace MSSA in all situations—just as penicillin-resistant *S. aureus* replaced penicillin-susceptible strains in the 1950s and 1960s.

Before pursuing the specific costs of MRSA and individual control strategies, it might be helpful to examine the general costs of MRSA overall, particularly when compared to MSSA. One study modelled estimates of the incidence, deaths, and direct medical costs of *S. aureus* infections in the New York metropolitan area in 1995 (Rubin *et al*., 1999). The study examined the relative impact of methicillin-resistant vs susceptible strains of *S. aureus* and of community vs hospital-acquired staphylococcal infections. The attributable cost of a patient with MRSA was approximately $2,500 higher than the attributable cost of a patient with MSSA ($34,000 vs $31,500). The higher cost of MRSA infections was due to the cost of vancomycin, longer hospital stay, and the cost of patient isolation procedures. For HAIs alone, the cost attributable to MRSA alone was approximately $3,700 higher on a per patient basis than the cost attributable to MSSA infections ($31,400 vs $27,700). MRSA infections also caused more deaths than MSSA infections (21% vs 8%) (Rubin *et al*., 1999). The study concluded that reducing the incidence of hospital-acquired MRSA and MSSA would reduce the overall societal costs from *S. aureus* infections.

Nearly 500 patients were included in a study assessing the impact of methicillin resistance on patients with *S. aureus* surgical site infection (Engemann *et al*., 2003). Patients infected with MRSA had a greater 90-day mortality rate and a longer stay in hospital than patients infected with MSSA. Median hospital charges were nearly $53,000 for MSSA infections and approximately $92,000 for MRSA infections. This resulted in a 1.19-fold increase in hospital charges overall and a mean attributable excess charge of nearly $14,000 for patients with MRSA infections, compared with MSSA patients ($p < 0.001$) (Engemann *et al*., 2003). Another study on patients with primary bacteraemias due to MRSA and MSSA similarly compared attributable hospital stay and total and variable direct costs of hospitalisation (Abramson and Sexton, 1999). This study showed that the median hospital stay due to MSSA bacteraemia was 4 days, compared with 12 days for MRSA. The median total cost for MSSA bacteraemia was $9,661 vs $27,083 for MRSA bacteraemia, that is, an approximate 3-fold increase in direct cost (Abramson and Sexton, 1999).

Prolongation of hospital stay is often used as a measurable index for the economic impact of acquiring MRSA in hospital (Abramson and Sexton, 1999; Engemann *et al*., 2003; Kim *et al*., 2001; Nathwani, 2003; Niederman, 2001b, Walker, 2002). Investigators highlight the importance of increased hospitalisation as a key determinant of the total cost of an episode of infection but it does not encompass all the components of the final bill (Nathwani, 2003). Wakefield *et al*. analysed the relative importance of laboratory, antibiotic, and per diem costs of caring for 58 patients with serious *S. aureus* infections (Wakefield *et al*., 1988). Laboratory costs accounted for 2%, antibiotic for 21%, and per diem costs for 77% of total infection related costs, with a greater proportion attributable to MRSA infections. Results of another study by Kim *et al*. confirmed the relatively marginal (4%) contribution of antibiotic costs to the overall cost of care in Canadian hospitals, but the final estimate for the cost of MRSA in Canadian hospitals approached $60 million each year (Kim *et al*., 2001).

The cost of eradicating MRSA with isolation, screening of patients, staff and the environment, topical clearance, and education was found to be approximately half that of treating a single MRSA bacteraemia (Rao *et al*., 1988). The incidence of hospital-acquired MRSA fell to zero in the 5 months following the implementation of these control strategies (Rao *et al*., 1988). Others have demonstrated that a strict MRSA policy is financially worthwhile (Hornberg *et al*., 2003; Pan *et al*., 2001; Vriens *et al*., 2002).

5. SPECIFIC COSTS OF MRSA

5.1. Costs of screening/surveillance cultures

Most hospitals have an MRSA screening policy of some description, usually for patients received from other hospitals, or for patients due to be admitted to a high-risk ward or for a high-risk procedure (Boyce, 1991). Some will also routinely screen patients from residential or nursing homes in the community, since these facilities frequently act as a reservoir for colonised patients (Fraise *et al*., 1997; Jernigan *et al*., 1995; Muder *et al*., 1991). Within the hospital, there are usually policies for screening patients involved in a cross-infection incident or outbreak, when new or unexpected cases are identified following routine laboratory investigation (Ayliffe *et al*., 1998). Such surveillance is deemed to be a useful control measure, since establishing carriage offers more rapid management of patients and their clinical area, including neighbouring patients and healthcare staff (Coello *et al*., 1994). Furthermore, inappropriate antibiotic therapy can be circumvented and future episodes of cross-infection averted. Regarding the former, prescribing a patient an antibiotic to which MRSA is resistant, encourages proliferation of the organism and increased risk

of invasive sepsis (Dancer, 2001). These patients are also more likely to shed the organism into the environment and onto others (Schentag *et al*., 1998).

Comprehensive screening policies for all admissions, however, are rare due to the increased time, effort, and resources required. Since most microbiology laboratories cannot confirm MRSA in less than 48 hr, clinicians often have to make their own decisions regarding the potential MRSA status of a patient and act accordingly. Screening samples would not generally be regarded as urgent and it is unlikely that they would be processed out-of-hours or over a weekend—thus adding further delay to the time of final report. Despite these difficulties, current opinion on the role of active surveillance cultures has been gaining momentum recently (Arnold *et al*., 2002; Farr and Jarvis, 2002). Infection control professionals are in agreement that screening patients for MRSA carriage is a useful procedure, because it is not possible to control what you don't know about (Farr and Jarvis, 2002).

While there are obvious benefits for hospitals and the individual from active surveillance, there should be an evaluation regarding cost benefits. One study found that the increase in hospital-acquired MRSA was associated with increased transfer of colonised patients from nursing homes and other hospitals (Jernigan *et al*., 1995). A subsequent cost–benefit analysis suggested that surveillance cultures of transferred patients would save between $20,000 and $460,000 and prevent from 8 to 41 HAIs due to MRSA (Jernigan *et al*., 1995). Such a screening programme would also reduce the number of patient-days spent in isolation. A more recent study showed that if early identification of colonised patients prevented transmission of MRSA to as few as six patients, then a screening programme would save money (Papia *et al*., 1999). The average cost of implementing recommended infection control measures for patients colonised with MRSA was approximately $5,235 per patient (laboratory and nursing costs) (Papia *et al*., 1999).

When MRSA eradication fails, or is never attempted, endemicity ensues. It is argued that in this situation, control efforts are no longer justified (Barrett *et al*., 1998). High rates of MRSA in an acute hospital, however, are associated with increased HAI rates, increased use of glycopeptides, higher risk of generating antibiotic-resistant Gram-positive bacteria, and additional healthcare costs (Herwaldt, 1999; Rubinovitch and Pittet, 2001). When the evidence in endemic hospitals is reviewed, containment efforts appear to decrease the incidence of MRSA HAIs (Rubinovitch and Pittet, 2001). Successful programmes are based upon early identification of the MRSA reservoir and prompt implementation of control precautions, particularly via the screening of high-risk patients on admission (Girou *et al*., 1998; Papia *et al*., 1999). This strategy has been shown to be cost-effective in a number of different acute-care endemic settings using varied cost indicators (Chaix *et al*., 1999; Jernigan *et al*., 1995; Papia *et al*., 1999; Rubinovitch and Pittet, 2001).

Targeted screening is similarly cost-effective (Girou *et al*., 2000). In one study of dermatology patients, it was shown that a selective strategy is cheaper because there are fewer samples submitted to the laboratory and less work imposed upon healthcare personnel (Girou *et al*., 2000). Another study involving neonates in an intensive care unit examined the cost benefits from active surveillance cultures and contact/droplet precautions for control of MRSA in the unit (Karchmer *et al*., 2002). Estimated costs of controlling a 10-month outbreak that resulted in 18 colonized and 4 infected infants in one unit ranged from over $48,000 to $68,000. The estimated excess cost of 75 MRSA bacteraemias in a second neonatal unit was $1,306,000; this outbreak included 14 deaths and lasted for over 50 months. The study concluded that weekly screening and isolation policies halted the outbreak in the first unit and cost 19–27-fold less than the attributable costs of MRSA bacteraemias in the second (Karchmer *et al*., 2002).

Recently, a performance improvement task force was set up to report best hospital practices for controlling MRSA (Arnold *et al*., 2002). The group looked at screening, isolation, cohorting, decolonisation, post-exposure follow-up, microbiology procedures, and surveillance methods, and categorised the recommendations into priority levels according to published data. Evidence for screening patients at risk of having MRSA was particularly strong, with most protocols receiving the top-level priority (strongly recommended and supported by well-designed epidemiological studies and experience) (Arnold *et al*., 2002). The group emphasised the need to increase patient screening. This was the first time that a public health department in the United States had stated that identification of the MRSA reservoir is necessary for effective control (Farr and Jarvis, 2002).

5.2. Handwashing

There is a huge amount of literature extolling the benefits of handwashing in the control of HAI (Larson, 1995). It is generally agreed that hand hygiene is the single most important activity in an infection control programme, but it is very difficult to get everyone to wash his or her hands routinely, particularly when the ward is busy or short staffed (Afif *et al*., 2002; Gopal Rao *et al*., 2002; Grundman *et al*., 2002). It is also difficult to cost the effectiveness of hand hygiene because it is not usually practised in isolation, but as part of an infection-control package (Harbarth *et al*., 2000). One recent study examined the effectiveness of a hospital-wide programme to improve compliance with hand hygiene (Pittet *et al*., 2000). The programme introduced bedside alcohol-based hand disinfection and monitored overall compliance with hand hygiene during routine patient care before, and during, the handwashing campaign. Surveys were performed over a 3-year period and HAIs were measured in

parallel. The study demonstrated a significant increase in compliance with hand hygiene (48–66%) over the study period, with concomitant decrease in the overall numbers of HAI and MRSA transmission rate. In particular, MRSA acquisition decreased from 2.16 to 0.93 episodes per 10,000 patient-days ($p < 0.001$). The consumption of alcohol-based hand rub solution represented extra costs of SFr 110,833, an average of SFr 101.15 per 1,000 patient-days. Total crude direct and indirect costs associated with the intervention were estimated as less than SFr 380,000. Given a conservative estimate of SFr 3,500 saved per HAI averted, prevention of 108 infections during the study period would have offset programme costs. In actual fact, it is possible that over 900 infections were prevented by the intervention (Pittet *et al*., 2000).

Others have noted a reduction in the proportion of hospital-acquired MRSA following the introduction of alcohol-based gel placed at the bedside (Gopal Rao *et al*., 2002). Different handwash products have similarly been associated with decreased numbers of patients acquiring MRSA (Reboli *et al*., 1989; Webster *et al*., 1994). One of these studies introduced the use of triclosan 1%w/v into a neonatal intensive care unit and reported elimination of MRSA from the unit (Webster *et al*., 1994). In addition, a reduction in the use of vancomycin resulted in a cost saving of approximately $A17,000 (Webster *et al*., 1994).

A sustained programme of educating clinical staff about MRSA and the benefits of hand hygiene was introduced at another hospital in order to cut costs (Nettleman *et al*., 1991). The transmission rate of MRSA was halved after assigning responsibility to medical and surgical residents on whose wards an MRSA isolate was identified. The programme was supplemented with handouts, bacteriological screening of staff hands, and feedback. Residents were encouraged to serve as role models for appropriate hand hygiene and other infection control precautions. These inexpensive interventions saved the hospital $42,000, or 115 hospital days, per year (Nettleman *et al*., 1991).

Despite the obvious benefits to patients, hospital staff do not wash their hands. Published standards for the control of HAI tend to focus upon the managerial and structural aspects of infection control but perhaps it is time for an explicit standard to be set on hand decontamination for all healthcare staff (Teare, 2000). Infection control teams can audit this (Pittet *et al*., 2000). Senior medical staff are role models and play a significant role in influencing hand hygiene compliance (Lankford *et al*., 2003; Teare, 2000).

5.3. Isolation, cohorting, and contact isolation

Patients may need source isolation because they are infected and hazardous to others, or they may need protective isolation because their susceptibility to

infection is increased. Such precautions against infection are often costly in money and the time of skilled staff and may be exasperating impediments to routine clinical work (Bagshawe *et al*., 1978; Barrett *et al*., 1998). Single room isolation may also precipitate psychological distress, particularly in the elderly (Tarzi *et al*., 2001). Cross-infection on wards, however, is difficult to prevent by routine measures, particularly if there is a staphylococcal disperser present. Both carriers and infected patients may heavily contaminate their immediate environment and release airborne particles carrying staphylococci (Boyce *et al*., 1997). Such patients should be isolated in a single room, if possible (Ayliffe *et al*., 1998).

Isolation is not generally practised without other basic hygienic procedures, so its impact on reducing staphylococcal spread in a hospital has to be assessed as part of an infection control package (Ayliffe *et al*., 1998). Furthermore, there are few, if any, studies examining the cost benefits of isolation as the single, or predominant, activity in control of MRSA. There is plenty of evidence, however, that isolation can facilitate control of endemic MRSA, including outbreaks and this in itself suggests that significant savings can be made from physically separating MRSA patients from others (Murray-Leisure *et al*., 1990; Shanson *et al*., 1985). In contrast, increasing the proximity of patients by adding a fifth bed to four-bedded bays significantly heightens the risk of cross-infection with MRSA (Kibbler *et al*., 1998). This supports the finding that the relative risk of MRSA acquisition increases with the colonization pressure from imported cases (Talon *et al*., 2003).

Hospitals can establish the use of specialised units with designated staff for control purposes (Fitzpatrick *et al*., 2000). An eight-bedded isolation unit in one large hospital was built specifically to control MRSA. The number of infections was more than halved in 2 years and further reductions occurred during the following 4 years (Selkon, 1980). A decrease in the spread of MRSA by use of isolation units was also observed in several London hospitals in the 1980s (Bradley *et al*., 1985; Dacre *et al*., 1986; Duckworth *et al*., 1988; Shanson *et al*., 1985). In contrast, a statistical model predicts that the risk of MRSA acquisition would increase by 160% per year in the absence of a dedicated cohort facility (Talon *et al*., 2003).

Hospitals without plentiful isolation facilities, or when overwhelmed with MRSA patients, have to be inventive when faced with control issues. Cohorting known positive patients together in ward bays is an option; if basic infection control practices are reinforced regularly, and there is access to flexible domestic support, spread of MRSA can be curtailed (Duckworth *et al*., 1988). Risk assessment regarding both patient and ward environment are helpful when considering control scenarios (Ayliffe *et al*., 1998; Wilson and Dunn, 1996). The establishment of an isolation facility on a temporary basis, however, may be required if the number of cases suddenly increases (Bradley *et al*., 1985; Cox *et al*., 1995).

Contact isolation is another control option for MRSA patients (Cohen *et al*., 1991; Jernigan *et al*., 1995), with or without cohorting (Arnold *et al*., 2002; Murray-Leisure *et al*., 1990). A theoretical cost–benefit analysis demonstrated that contact precautions could decrease the total days of MRSA isolation by 42%, prevent 8–41 infections each year, and decrease hospital costs by over $20,000 (Jernigan *et al*., 1995). Even the cost of gowns used for contact precautions can be reduced following the introduction of a programme of active surveillance cultures and immediate contact isolation for new ICU admissions (Muto *et al*., 2003). In the first 3 months of this particular programme, the incidence rate of MRSA decreased from 5.4 per 1,000 patient-days to 1.6 per 1,000 patient-days, while overall gown use decreased by 40% (Muto *et al*., 2003).

Contact isolation does not always control hospital-acquired MRSA, however, particularly if there is understaffing, unidentified carriers, unusual modes of transmission, or high carriage rates among patients on admission (Herwaldt, 1999). Infection control staff need to identify the reasons for persistent transmission and target their interventions specific to local circumstances (Herwaldt, 1999). Control can be achieved through a multifaceted approach, even in endemic situations. Patient cohorting, respiratory or contact isolation precautions, use of an isolation ward, and a hand hygiene programme significantly reduced the transmission of MRSA in one acute hospital (Herwaldt, 1999). The proportion of MRSA isolates decreased from 32% to 22%, the number of MRSA carriers was halved in 1 year and the rate of MRSA infections decreased from 2% to 0.2%. Furthermore, vancomycin expenditure decreased from $32,000 to $12,500 a year, saving the hospital $19,500 (Herwaldt, 1999).

5.4. Laboratory costs

Laboratory costs from HAI are often ignored because attention is more likely to be focused on the direct costs relating to patients, that is, treatment costs and extra days spent in hospital (Wakefield *et al*., 1988). Extra specimens from HAI patients, however, provide an increasing drain on laboratory resources. Both clinical and environmental samples require uplift to the laboratory, which may not be in site, followed by registration, processing, and reporting. Often the finding from one specimen generates a request for more, either from the same patient or from others. HAI are likely to be associated with multiple resistant organisms, which themselves cause extra work due to extended susceptibility testing. They may also require additional tests, including molecular typing at reference laboratories. The cost of such specialist attention is most unlikely to be included in the final total.

Plowman *et al*. examined the cost ratios of microbiology tests from hospital patients with and without HAI (Plowman *et al*., 2001). The mean cost incurred for non-HAI patients was £6.97, compared with £33.13 for patients with HAI. Thus, microbiology tests from HAI patients were nearly five times more expensive than those from non-HAI patients. Other pathology tests gave a cost ratio of 2.3 between non-HAI and HAI patients, that is, more than twice as expensive for HAI patients. The overall percentage contribution from microbiology tests towards the total cost of HAI was 0.83%; all laboratory tests accounted for nearly 3% (Plowman *et al*., 2001).

The latter study investigated the rate and cost of all HAI occurring in an English district general hospital, so the proportion of patients with MRSA was unknown. A study specifically examining the cost of serious *S. aureus* infections, including MRSA, analysed the relative importance of laboratory and antibiotic costs and extra days spent in hospital (Wakefield *et al*., 1988). Per diem costs were 77% of total infection-related costs, antibiotics contributed a further 21%, and laboratory costs accounted for just 2% of the final total. Not unexpectedly, extra days in hospital due to HAI contributed most towards the total.

Laboratory costs included bacterial cultures, antibiotic susceptibility testing, and antibiotic serum levels, with labour and consumables already incorporated (Wakefield *et al*., 1988). They were calculated by multiplying the number of tests by the direct cost per test. Indirect costs, such as overheads and equipment, were not included. Also ignored were non-microbiological tests, such as white blood cell counts and renal function tests. The final total associated with treating 58 serious *S. aureus* infection gave an overall mean of $66.72. The mean laboratory cost for 48 patients with MSSA infections was $61.74, compared with $92.73 for 10 patients with MRSA infections ($p > 0.05$) (Wakefield *et al*., 1988).

Other previously mentioned studies have considered laboratory costs as part of an MRSA screening programme (Jernigan *et al*., 1995; Karchmer *et al*., 2002; Papia *et al*., 1999; Rubinovitch and Pittet, 2001), although it is not always clear exactly which components of laboratory processing were used in the final estimate. There are several different MRSA screening methods, with varying degrees of cost-effectiveness (Kunori *et al*., 2002).

Some laboratories have been driven to incorporate more expensive molecular tests, such as the polymerase chain reaction (PCR), because these tests can identify selected organisms significantly faster that conventional culture (Martineau *et al*., 1998). They can also detect smaller numbers of these organisms with reliable specificity (Tokue *et al*., 1992). Such techniques have the potential to markedly improve patient management, while also reducing the risk of cross-infection and even outbreaks. Unfortunately, the cost of introducing and maintaining this technology is prohibitive for most laboratory budgets. PCR testing, however, has been shown to be an accurate and cost-effective

method for identifying patients with *S. aureus* (Jayaratne and Rutherford, 1999; Shrestha *et al*., 2003). The total cost for PCR per test has been quoted as $3.62, compared with $4.77 for conventional culture, with an average turnaround time of 48 hr compared with 82 hr for culture (Jayaratne and Rutherford, 1999).

5.5. Antibiotic costs

It is generally agreed that the use of antibiotics has selected for resistant organisms from initially susceptible populations and further use has encouraged the subsequent proliferation witnessed today (Schentag *et al*., 1998). While any antibiotic has the propensity to select for a resistant strain, there are some classes that are more likely to be associated with MRSA (Dancer, 2001; Hill *et al*., 1998; Hori *et al*., 2002; Monnet, 1998; Monnet and Frimodt-Moller, 2001; Venezia *et al*., 2001). The consequence is clinically significant infection with an organism for which there are few treatment options (Dancer, 2003). Those antibiotics, which might be expected to be effective, tend to be expensive and toxic (Dancer, 2003; Janknegt, 1997). It is likely that the cost of using and monitoring such drugs for MRSA provide a significant contribution towards overall HAI costs (Casewell, 1995; Rao *et al*., 1988; Vriens *et al*., 2002). Conversely, decreasing overall antimicrobial use and/or improving the quality of antimicrobial prescribing might be expected to lower the cost of pharmaceuticals for HAI (Geissler *et al*., 2003; Landman *et al*., 1999).

The study by Plowman *et al*. also examined the antimicrobial costs for HAI (Plowman *et al*., 2001). Antimicrobials accounted for a mean cost of £13.40 for non-HAI patients, compared to £71.07 for HAI patients. The percentage contribution towards the overall costs of HAI was 1.83%. The contribution from antibiotics towards costs of serious *S. aureus* infection, however, was shown to be 21% in a separate study (Wakefield *et al*., 1988). The same study examined antibiotic costs for both MSSA and MRSA, and found that mean costs for MSSA accounted for $612.53 compared with $1067.52 for MRSA. Adverse complications of antibiotic therapy were not investigated, but the authors postulated that the requirement for parenteral therapy for MRSA contributed towards the number of additional drugs in hospital for MRSA patients (mean 19.1 days) compared to patients with MSSA (mean 5.9 days) ($p < 0.004$) (Wakefield *et al*., 1988). MRSA outbreaks also have the potential for driving up drug costs. A 5-week outbreak involving five wards consumed £6,440 worth of teicoplanin, almost half the total cost attributed to the outbreak excluding labour costs and extra days in hospital (Mehtar *et al*., 1989).

It seems reasonable to examine the potential for savings from infection control policies and programmes regarding the use of antibiotics (Mehtar, 1993, 1995). The role of the medical microbiologist includes giving advice on antimicrobial therapy, encompassing choice, dose, length of course, route, toxicity,

combinations, and monitoring. Timely and appropriate advice on the management of infected patients can contribute significantly towards cost savings. Without microbiological guidance, it was shown that antibiotic usage increased by £2,000 per month, compared with a similar period in the previous year (Mehtar, 1995).

The implementation of antibiotic policies has been shown to be cost-effective (Geissler *et al*., 2003; Mehtar, 1993). Such policies can be extended to formulary restrictions and physician monitoring (Landman *et al*., 1999; Woodward *et al*., 1987). Strictly enforced restrictions for aminoglycosides, cephalosporins, and vancomycin generated combined savings of $2.61 per antibiotic day ($p < 0.0046$) and $34,597 per month ($p < 0.0003$) (Woodward *et al*., 1987). A retrospective analysis of 322 patients with bacteraemia, treated before and after the onset of controls, revealed that antibiotics were more appropriately used afterwards (Woodward *et al*., 1987). Another study examined both cost savings and the effect on HAI organisms after the introduction of an antimicrobial-prescribing improvement programme (Frank *et al*., 1997). Over a two-year period, antibiotic prescribing decreased from nearly 160,000 to 140,000 defined daily doses, with concomitant savings of $280,000 in the first year and $390,000 in the second (Frank *et al*., 1997). These accompanied significant decreases in the rates of enterococcal and selected Gram-negative bacteraemias and in the rates of MRSA and Stenotrophomonas colonisation and infection (Frank *et al*., 1997).

Antibiotic consumption is particularly high in the Intensive Care Unit. This offers an opportunity for implementing and evaluating policies designed to emphasize more rational use of antibiotics (Gruson *et al*., 2000). Implementing such a policy in an 11-bedded ICU over a 5-year period resulted in a significant reduction in MRSA and ceftriaxone-resistant Enterobacteriaceae, while costs showed a progressive decrease from €64,500 to €42,000 in the final year (Geissler *et al*., 2003).

The requirement for parenteral administration of glycopeptides precipitates the extended hospital stay and associated costs for MRSA patients (Janknegt, 1997). Strategies to circumvent this have been introduced, namely outpatient programmes utilising once-daily teicoplanin administration and earlier switching from iv to oral routes if possible (Janknegt, 1997; Nathwani, 2001, 2003; Neiderman, 2001b). An economic evaluation of linezolid, flucloxacillin and vancomycin in the empirical treatment of cellulitis suggested that use of linezolid alone would result in a higher overall success rate and would be less costly than vancomycin across the entire spectrum of the patients' risk of being infected by a resistant pathogen (Vinken *et al*., 2001).

Other relatively simple policies benefit both patients and budgets (Jewell, 1994; Rubinovitch and Pittet, 2001). A decrease in vancomycin expenditure from $32,000 to $12,500 per year occurred following the introduction of contact

precautions, isolation, and a hand hygiene programme (Herwaldt, 1999). Even the targeted application of nasal mupirocin can demonstrate cost savings through the lesser numbers of patients who go on to develop MRSA sepsis (Bloom *et al*., 1996; van den Burgh *et al*., 1996). The huge difference in the cost of newer antibiotics for Gram-positive infections will provide a significant impact in prescribing budgets, should glycopeptide-resistant *S. aureus* flourish (Muto *et al*., 2003). The parenteral streptogramin, Synercid®, and the oxazolidanone, linezolid, cost at least five to seventeen times more than vancomycin (Muto *et al*., 2003).

5.6. Cleaning

The importance of hospital cleaning in the control of MRSA, as with so many other control components, is still unclear (Dancer, 1999a). Much is known about the epidemiology of *S. aureus* and its potential to contaminate the environment (Boyce *et al*., 1997; Layton *et al*., 1993), but it is not known what proportion of patients acquire their MRSA directly, or indirectly, from a contaminated environment. It seems likely that falling standards of hygiene in hospitals have contributed towards increasing rates of MRSA; lack of evidence, however, means that its role in reducing infection remains contentious, let alone evaluated for potential savings within an HAI control programme. One recent study, however, concluded that vigorous environmental cleaning helped to control an MRSA outbreak, along with other control measures (Rampling *et al*., 2001). Preintervention, nearly 70 patients acquired E-MRSA 16 on a male surgical ward over a period of about 20 months. Environmental cultures provided indistinguishable strains. The domestic cleaning time was then doubled, with emphasis on removal of dirt by vacuum cleaning and allocation of responsibility for the routine cleaning of shared medical equipment. In the 6 months that followed, only three patients acquired the epidemic strain and monthly surveillance cultures failed to detect it in the environment. A cost analysis showed that the cleaning initiative saved nearly £28,000 (Rampling *et al*., 2001).

It is likely that cleaning is a cost-effective method for MRSA control, but lack of evidence should not be used as an excuse for the continued erosion of domestic services (Dancer, 2002). Neither should the requisite evidence be mandatory before improving cleaning standards in healthcare premises (Talon, 1999). There is little point in educating healthcare workers to wash their hands before and after patient contact, when the first item they touch after washing recontaminates their hands once again (Dancer, 2002).

5.7. Outbreaks

Strains of MRSA may be epidemic in character, affecting two or more patients to cause episodes of cross-infection or even outbreaks. Molecular typing

techniques demonstrate transmission within and between healthcare facilities in cities, countries, and across continents (Ayliffe, 1997; Witte *et al*., 1997). When a clearly defined outbreak occurs in hospital, there is an opportunity for costing the incident; it is much more difficult to estimate the costs of endemicity. Such analyses offer strong support for prompt control measures, since they invariably show significantly increased costs (Mehtar, 1993). Even a limited cross-infection episode can be expensive. One particular incident on an orthopaedic ward was estimated to cost an extra £7,321, excluding physiotherapy and X-ray, following MRSA transmission between a long-term patient with a chronic ulcer and a patient who had just received a prosthetic knee implant (Mehtar, 1993).

Larger outbreaks generate even greater costs. A 5-week outbreak in 1986 involving five wards cost nearly £13,000 but this did not include labour or extra days in hospital (Mehtar *et al*., 1989). More recently, an outbreak involving more than 400 patients in England was estimated to be in excess of £400,000 of which the provision of isolation wards accounted for a large proportion (Cox *et al*., 1995).

The costs of not controlling MRSA are much greater than the costs of control (Casewell, 1995; Karchmer *et al*., 2002; Rao *et al*., 1988). The analysis of a large outbreak in Madrid suggested that the extra costs incurred exceeded £700,000 (Ayliffe *et al*., 1998; Casewell, 1995; Coello *et al*., 1994). It was thought that the extra length of stay and escalating use of vancomycin required for routine prophylaxis were the main contributors towards excess costs.

Even simple procedures such as screening, isolation, and cleaning could potentially save thousands of pounds if an outbreak is averted. A 10-month outbreak in a neonatal SCBU was estimated to cost approximately $49,000–69,000 compared with a similar SCBU, which did not receive any of the basic control interventions implemented in the first SCBU. The second unit witnessed 14 deaths in the outbreak, which lasted more than 50 months and cost $1,307,000 (Karchmer *et al*., 2002). Doubling the cleaning on a male surgical ward, as already described, eradicated an epidemic strain of MRSA and saved over £28,000 (Rampling *et al*., 2002).

5.8. Intensive care unit

ICUs are unique because they house seriously ill patients who require constant hands-on care in a confined environment. These patients are commonly exposed to high concentrations of antibiotics (Kollef and Fraser, 2001). This results in the emergence and spread of antibiotic-resistant bacteria, which create additional costs to the overall total generated by intensive care (Geldner *et al*., 1999; Niederman, 2001a, b; Pittet *et al*., 1994). Acquisition of MRSA in this environment is strongly and independently influenced by colonisation pressure (Merrer *et al*., 2000). Anything that might reverse this pressure,

therefore, should have a significant impact on the cost of managing MRSA in the ICU.

In one 26-bedded medical ICU, an infection control programme with selective screening significantly reduced the incidence of ICU-acquired infection or colonisation (from 5.6 to 1.4 per 100 admissions) over a 4-year period despite a persistently high (4%) prevalence of MRSA carriage among newly admitted patients (Girou *et al*., 1998). A cost–benefit analysis showed that the mean cost attributable to MRSA infection was $9,275, compared to the total costs of a control programme ranging from $340 to $1,480 per patient. The study demonstrated that a 14% reduction in MRSA infection rate resulted in the control programme being beneficial (Chaix *et al*., 1999). A similar study utilising universal screening was also shown to be cost-effective (Lucet *et al*., 2003).

Other cost-effective strategies include the rational use of antibiotics in the ICU. In a study already mentioned, an antibiotic-use policy demonstrated a reduction in antibiotic-selective pressure, MRSA and other resistant organisms and a progressive reduction in costs (100% for 1994, 81% for 1995, 65% for 1998) (Geissler *et al*., 2003). It stands to reason that combining as many of these strategies as possible is likely to have a significant impact on the rates of MRSA colonisation and infection, as well as reducing the high costs required for management. Once again, the costs of control are offset by savings from lesser numbers of infected patients (Chaix *et al*., 1999; Khan and Celik, 2001; Lucet *et al*., 2003; Rubinovitch and Pittet, 2001).

5.9. Community/long-term care

Early discharge of infected or colonised patients to convalescent homes, or to homes for the elderly, has created an expanding reservoir of MRSA in the community (Boyce, 1998; Fraise *et al*., 1997; Jewell, 1994; Muder *et al*., 1991). Patients with MRSA in the community may not receive so much attention as those in hospital because their environment is regarded as relatively low risk (Dancer, 1997). Colonised patients in low dependency units, however, have four times the clinical infection rate of uncolonised patients (Muder *et al*., 1991). The cost of managing long-term care patients with MRSA is almost twice as expensive as managing patients with MSSA (Capitano *et al*., 2003). There are also treatment difficulties, since active infection with MRSA may require parenteral therapy and there are few oral options (Dancer, 2003; Nathwani, 2001).

Aggressive containment strategies can reduce the MRSA infection rate in nursing homes. In one study, the initial colonisation rate in residents in a 42-bedded extended care unit/nursing home was 52%, but dropped to 2%, with an infection rate of 1.4%, following a programme of screening, contact isolation, topical clearance, and treatment of infected patients

(Jacqua-Stewart *et al*., 1999). The process was shown to be cost-effective (Jacqua-Stewart *et al*., 1999).

MRSA is not solely hospital-acquired (Boyce, 1998; Herold *et al*., 1998; McLaws *et al*., 1988); new strains are appearing, some characterised by glycopeptide resistance and others by specific virulence determinants such as the PVL gene (Dufour *et al*., 2002; Hiramatsu, 2001). Such evolutionary changes do not bode well for the future, whereby the costs from untreatable infection could be incalculable.

6. CONCLUSION

Rising healthcare costs have become an increasing concern to everyone involved in delivering healthcare services (Robinson, 1993). It is no longer appropriate for infection control to be regarded merely as a programme for self-improvement, or as a commendable marker of quality, but as a necessary, critical and cost-effective activity (Duffy, 1985). It should receive strong support from seniors, managers, and any others who might influence healthcare budgets (Brachman and Haley, 1981; Casewell, 1995; Jarvis, 1996). Infection control programmes are, without doubt, cost-effective, but if preventive care is to be encouraged, financial incentives for the value of benefits received require continued emphasis and evaluation (Miller *et al*., 1989). It is almost as difficult to cost an event that does not happen (Duffy, 1985), as it is to motivate managers faced with bed pressures and waiting lists, especially when they do not understand the epidemiology of infectious organisms or the potential benefits of infection control (Anon, 1985).

There has been some debate on the type and extent of MRSA control measures, particularly in endemic hospitals (Barrett *et al*., 1998; Boyce, 1991). Accordingly, widely divergent strategies have been employed, from "search and destroy" to almost complete complacency (Barrett *et al*., 1998; Spicer, 1984). There is, however, mounting evidence that even simple control procedures impact upon the rate of MRSA acquisition and save considerable sums of money (Arnold *et al*., 2002; Chaix *et al*., 1999; Pittet *et al*., 2000; Rampling *et al*., 2001). Complacency in the face of endemic MRSA is thus unwarranted and, frankly, irresponsible (Dancer, 1999b; Farr and Jarvis, 2002). In addition, there are the societal and human costs of MRSA infection, almost impossible to evaluate and, for the most part, completely ignored (Drummond *et al*., 1989; Engemann *et al*., 2003; Jönsson and Lindgren, 1980; Karchmer *et al*., 2002; Romero-Vivas *et al*., 1995). Complacency towards MRSA from the human perspective should be regarded as unethical, particularly if the cost of controlling MRSA is balanced against the "cost" of an MRSA death (Dancer, 1999b).

Physicians have an obligation towards their patients' safety (Scolan *et al*., 2000). Hospital admission, whether for routine or emergency treatment, should not routinely include the acquisition of MRSA. Such an outcome has the potential to elicit legal interest, since there are burgeoning cost implications from malpractice and adverse events (Korin, 1993; Olson, 1981; Scolan *et al*., 2000). Successful litigation is yet to occur in the United Kingdom, but increasing patient and media interest in hospital hygiene and the "superbug" has already initiated legal activity (BBC Scotland, 2003).

From the evidence presented in this chapter, it is clear that a programme for preventing HAI will not only pay for itself but will also generate other direct and indirect benefits to patients and society as a whole (Khan and Celik, 2001; Rubin *et al*., 1999). In view of the global threat from multiple resistant organisms, an effective infection control programme could be one of the most cost-beneficial medical interventions available in modern public health (Wenzel, 1995).

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