Methicillin-resistant *Staphylococcus aureus* (MRSA) has been an increasing problem since its isolation in England in 1961. The publicity surrounding MRSA, and nosocomial infection in general, has never been greater. The introduction by the Department of Health in the United Kingdom of mandatory surveillance schemes for both MRSA bacteraemia and surgical site infection (SSI) in orthopaedic surgery from 2001 and 2004, respectively, highlights the importance of nosocomial infection. Our aim is to examine the rising problem of infection with MRSA and its associated economic implications. Current practice in the UK combined with a literature review have been undertaken in order to provide further suggestions for the lowering of rates of infection particularly from the perspective of orthopaedics and trauma.

**The current problem**

The prevalence of MRSA has continued to increase for most of the past 15 years. There are, however, great variations between countries and, in general, there is a north-south gradient. Scandinavia, The Netherlands and Germany have low rates; Italy, Spain and Turkey have the highest rates with France and the United Kingdom in the middle. Voss et al reported the level of methicillin resistance in *Staph. aureus* isolates to be between < 1% in Scandinavia and > 30% in Spain, France and Italy. Other studies have reported similar variations, with rates of 2% in The Netherlands and Switzerland compared with 54% in Portugal and between 43% and 58% in Italy.

The European Antimicrobial Resistance Surveillance System (EARSS) routinely collects generated antimicrobial susceptibility testing data from more than 700 laboratories serving 1100 hospitals in 28 European countries. Data have been collected since 1999 and include the antimicrobial susceptibility to *Staph. aureus*. The overall EARSS network catchment population is more than 100 million European inhabitants. Between 1999 and 2002 there was a significant increase in the prevalence of MRSA (p < 0.05) in Austria, Belgium, Germany, and the UK. The prevalence is at least 10% in most European countries, rising to 40% to 50% in some cases.

The latest figures for the UK show a fairly static picture, with rates of approximately 40% for the past three years. The total number of staphylococcal infections, however, has increased recently with the rate of MRSA bacteraemias also increasing by 3.6%.

While there are few data specifically relating to MRSA within orthopaedics and trauma, De Lucas-Villarrubia et al showed the prevalence of MRSA to be 1.6% within an orthopaedic department compared with 0.3% within the general hospital setting. Tai et al reported similar results, with 1.6% of the total orthopaedic admissions to a London teaching hospital being either infected with or colonised by MRSA. The SENTRY study showed that although the overall numbers of staphylococcal infections within an orthopaedic setting were low in comparison with those in general medicine or intensive care, the level of methicillin resistance was high.

Recent data collected in the surgical-site infection module of the Nosocomial Infection National Surveillance Service (NINS) reported 4351 infections after 107,492 operations in 12 clinically similar categories of procedure. The risk of developing surgical-site infection varied with the type of surgery. Limb amputation and bowel procedures were associated with the greatest risk. Of the micro-organisms causing infection, 49% were staphylococci, of which 81% were *Staph. aureus*. Of these, 63% were resistant to methicillin.

**MRSA – genetics and spread**

Methicillin resistance in staphylococci is caused by the presence of an acquired penicillin-binding protein, PBP2a. This protein is encoded by the gene mecA which is carried on the staphylococcal chromosomal cassette. Levels of resistance of the staphylococci depend...
upon the production of PBP2a. Hospital-acquired, and the more recently recognised community-associated MRSA, are thought to differ genetically. Five accepted clonal lineages for hospital-acquired MRSA have been defined. These have been classified as the Iberian, Brazilian, Hungarian, New York/Japan and Paediatric pandemic clones. Although resistance to all known antibiotics has developed within these genotypes, a community-associated MRSA strain has been recently recognised which is typically only β-lactam-resistant. The exact origins of community-associated MRSA are debatable but, unlike its hospital counterpart, community-associated MRSA tends to affect groups with few or no risk factors, e.g. children.

Cost implications of MRSA
The cost implications of hospital-acquired infection are enormous. One in 12 patients will develop such an infection. A study by the Department of Health in 1995 demonstrated that patients with one or more hospital-acquired infections incurred costs which were 2.9 times greater than those for uninfected patients. The costs in orthopaedic practice were 2.6 times greater. Other economic issues extend beyond the hospital setting and, nationally, it is estimated that patients who acquire an infection in hospital take an additional 8.7 million days to return to work. The actual additional cost varies with different studies and can be as high as US$3800 per patient.

In Kettering, UK, the cost of containing an outbreak of more than 400 patients was thought to be greater than £400 000. Orthopaedic infections are particularly expensive to treat. Nathwani divided the costs into three elements; those to the patient, those to the hospital and those to society (Table I).

Hospital costs have been further broken down by Plowman et al, who calculated the additional costs for an episode of hospital-acquired infection. Hospital overheads, nursing care and treatment costs were the most important, accounting for almost 80% of the additional expense.

Risk factors for MRSA
Since MRSA is acquired by spread, proximity and contact with other colonised patients are thought to be predominant risk factors. For similar reasons, a prolonged hospital stay or an earlier hospital admission is also implicated. Table II lists the most important risk factors.

Prevention and prophylaxis
With the increasing prevalence of MRSA, prevention has never been more important. This is achieved by a variety of methods, ranging from simple hand hygiene to isolation and widespread screening.

Methods of infection control. There are many theories on the best way to control resistant bacteria often requiring expensive antibiotics and costly isolation and screening. Despite this, basic measures for the control of infection such as hand hygiene, ward cleaning and high standards of aseptic techniques are essential. Recently, the media has focused on the general cleanliness of hospitals and has suggested a direct link between this and the spread of MRSA. Hospital cleaning services have certainly been targeted for cost-cutting within the National Health Service. Despite the fact that Staphylococcus is often found in hospital dust and that MRSA has been isolated from inanimate objects such as television sets and computer keyboards, there is little evidence to link dirty hospitals with the rise in hospital-acquired infection with MRSA. Hand hygiene is thought to be the cornerstone of the prevention of MRSA infection and an alcohol-based hand rub has frequently been shown to be effective against hospital-acquired MRSA infection. Despite this as well as the publication of guidelines, compliance is estimated to be less than 50%.
There are many reasons for non-compliance, which range from simple forgetfulness to a lack of knowledge about the guidelines, insufficient time, high workload and understaffing. Placing hand-hygiene dispensers at every bed space may overcome some of these issues.

**Chemoprophylaxis.** The prevalence of MRSA is exacerbated by rising levels of nasal carriage. As early as the 1940s attempts were made to eradicate nasal carriage, mainly with antiseptic snuffs and many agents have since been used. These range from oral antibiotic solutions such as either trimethoprim-sulfamethoxazole with rifampicin, minocycline with rifampicin, or nebulised solutions. The last have little or no effect.

To date, the most effective treatment of intranasal colonisation by MRSA is the application of mupirocin ointment. Reagan et al studied two groups of medical personnel who were known to have colonisation by MRSA. One group was given mupirocin ointment, while a control group was given a placebo ointment. Initially, there was a dramatic fall in colonisation in the mupirocin group although this was partially offset by a recolonisation rate of approximately 30%. Other studies have shown more promising results. Wilcox et al studied patients on three orthopaedic wards who were scheduled to undergo orthopaedic surgery which required the insertion of metal prostheses. Peri-operative prophylaxis involved nasal mupirocin for five days and a bath with triclosan on the day of surgery. The number of MRSA, surgical site infections was monitored over the following six months and compared with the two previous six-month periods. A marked decrease in the incidence was noticed, from 23 per 1000 operations to between 3.3 and 4 per 1000 operations (p < 0.001). The level of surgical site infection caused by other pathogens remained unchanged and the rate for the following two years remained low.

Although another trial in elective orthopaedic patients undergoing prosthetic insertion failed to show a significant decline in SSI, other studies have shown significant reductions in infections with *Staph. aureus* after the use of intranasal mupirocin in dialysis patients and in patients undergoing cardiothoracic surgery and, possibly, upper gastrointestinal surgery. A prospective, randomised trial by Harbarth et al showed the synergistic effect of nasal mupirocin and chlorhexidine baths. A group of 102 hospitalised patients was given chlorhexidine baths combined with either nasal mupirocin or a placebo. Colonisation by MRSA was eradicated in 25% of the mupirocin group compared with 18% of the placebo group.

With widespread use comes resistance. After a study lasting 4.5 years in a Veterans Administration hospital and long-term care facility, in which mupirocin was used to reduce the colonisation rates in an endemic population, Vasquez et al demonstrated that of the 632 MRSA isolates 126 showed some resistance to mupirocin. Their recommendation was to avoid the widespread use of mupirocin ointment when MRSA was endemic. This is supported by the current guidelines in the United Kingdom which recommend the use of mupirocin and antiseptic detergents such as 4% chlorhexidine or 2% triclosan for patients who are found to be carrying MRSA at any site. The guidelines recommend that evidence of persistent colonisation should be managed by repeat treatment, but that prolonged treatment should be avoided in order to prevent increased resistance. However, recent long-term follow-up data have shown that short-term peri-operative prophylaxis in orthopaedic surgery has not resulted in the development of resistance to mupirocin.

For orthopaedic operations in which prosthetic implants are to be used, peri-operative systemic prophylactic antibiotics are vital. Although cephalosporins are widely used, they are of little or no use in preventing infection with MRSA. The use of glycopeptides is controversial. Although some authors consider that their use should be restricted in order to prevent the increasing resistance of MRSA, others feel that teicoplanin is a reasonable choice if there is thought to be a high risk of infection with MRSA. Current recommendations suggest that the use of glycopeptides should be restricted to those patients who are colonised by MRSA, or in units which have experienced previous problems with the organism.

**Physical prophylaxis.** Physical methods in combination with chemoprophylaxis are used in many hospitals to prevent the spread of MRSA. Isolation is often used and, although some reports show mixed results, most evidence supports such a measure.

Many reports have focused on controlling epidemics of MRSA rather than the control of endemic MRSA. Guidelines from the British Society for Antimicrobial Chemotherapy and the Society for Healthcare Epidemiology of America recommend active surveillance for MRSA in high-risk patients and isolation for those found to be colonised or infected. The guidelines in the United Kingdom for the control of MRSA are more detailed and specify the requirements of isolation. An isolation ward with hand wash basins and toilet facilities in every room has been advocated while the use of side rooms, often used as an alternative to isolation may be less effective. It appears that the risk of transmission is lower for those patients in isolation compared with those who are not. Jernigan et al noted an almost 16-fold decrease in the rate of transmission of MRSA once isolation precautions had been introduced. Farrington et al maintained low numbers of MRSA cases over ten years with active screening of high-risk patients and staff, isolation in single rooms, eradication and ward closures. With increasing workload and pressure because of ward closures, these precautions were relaxed. The number of cases of infection with MRSA rose as a result. For isolation procedures to be effective they should be combined with active surveillance cultures of high-risk patients, hand hygiene and the treatment of healthcare workers implicated in the transmission of MRSA.

A study by Biant et al combined many of the above features to good effect. All elective orthopaedic patients in a
### Table III. Suggested protocol for the identification of MRSA carriage and the treatment of an established infection

<table>
<thead>
<tr>
<th>1)</th>
<th>Strict adherence to national guidelines for screening in high-risk areas with:</th>
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<tbody>
<tr>
<td>a)</td>
<td>Screening on admission for all regional/national referral centres, while high-risk areas should screen the following patients: those known to be previously affected or colonised; frequent readmissions; those transferred from MRSA-infected wards or nursing homes; and those transferred from hospitals abroad.</td>
</tr>
<tr>
<td>b)</td>
<td>Discharge screening.</td>
</tr>
<tr>
<td>c)</td>
<td>Screening of the nose, perineum, skin lesions and manipulated sites of all other patients after a single case has been detected.</td>
</tr>
<tr>
<td>d)</td>
<td>Isolation of carriers.</td>
</tr>
<tr>
<td>e)</td>
<td>Screening of all staff if additional cases occur.</td>
</tr>
<tr>
<td>f)</td>
<td>Isolation of patients before negative swab results have been received. On identification of positive swab cultures for MRSA, the patients should be kept in isolation.</td>
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<tr>
<th>2)</th>
<th>Treatment of carriers as outlined in the national guidelines with:</th>
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<tbody>
<tr>
<td>a)</td>
<td>The use of nasal mupirocin for five days, repeated if further swabs show persistent colonisation.</td>
</tr>
<tr>
<td>b)</td>
<td>Bathing in antiseptic detergents such as 4% chlorhexidine or 2% triclosan for patients carrying MRSA at any site. This may be repeated if the strain is not eradicated.</td>
</tr>
<tr>
<td>c)</td>
<td>Application of hexachlorophane powder to the axilla and groin, if they are thought to be colonised.</td>
</tr>
<tr>
<td>d)</td>
<td>Treatment of throat carriers is not required but, if undertaken, this normally requires systemic treatment with rifampicin and fusidic acid, or ciprofloxacin.</td>
</tr>
</tbody>
</table>

| 3) | Administration for five days of nasal mupirocin in combination with a triclosan bath on the day of surgery to all patients scheduled to receive implanted prosthetic material. |

| 4) | Education of nursing and medical staff on hand hygiene which is effective, although compliance is poor. |

| 5) | Treatment of an established infection initially with vancomycin while the patient is in hospital. Teicoplanin or linezolid can then be given on an outpatient basis. The length of administration should be decided by the treating clinician. |

district general hospital were subject to simple measures for control of infection combined with ring fencing of elective orthopaedic beds. No trauma patients were admitted and all patients were swabbed for MRSA before being admitted. No patient with a previous or current colonisation history of MRSA was admitted to the ward. The incidence of post-operative infections decreased from 43 in 417 to 15 in 488 (p < 0.0001) with no new cases of infection by MRSA being detected in arthroplasty patients in the two-year period. Although this policy allowed an increase in the total number of arthroplasties to be performed over the given period, there were few data on the cost-effectiveness of such isolation policies, a fact highlighted by Cooper et al.\(^\text{65}\)\

### Screening and its cost-effectiveness

Many screening methods have been used in order to identify patients who are infected with MRSA. To date, however, there have been few studies which detail the cost-effectiveness of these methods. Current guidelines in the United Kingdom\(^\text{57}\) suggest that for high-risk areas of the hospital (orthopaedic, vascular and cardiothoracic wards and intensive care) and regional and national referral centres, the following should be undertaken: 1) admission screening; 2) discharge screening; 3) screening of all other patients after a single case is detected; 4) isolation of carriers; and 5) screening of all staff if additional cases occur.

Kunori et al.\(^\text{66}\) described a mathematical model to determine the cost-effectiveness of various screening techniques. The effectiveness of the test was based on its sensitivity, specificity and the time taken to obtain a result. This was divided by the cost for each test in order to determine a cost-effectiveness ratio. It was found that the most cost-effective screening site was the nose, followed by the perineum and skin. Combination sampling was better, with the best results being obtained from nose and wound swabs. The best laboratory test for staphylococcal identification was the Pastorex Staph-Plus test (Sanofi Diagnostic Pasteur, Marnes-la-Coquette, France), although the BBL Crystal MRSA ID (Becton Dickson, Oxford, UK) proved to be the most effective method of determining susceptibility to methicillin.\(^\text{69}\) Other laboratory identification tests which used selective incubation media gave poor results, while direct identification by polymerase-chain-reaction techniques proved to be highly sensitive, with a rapid identification time, but were less cost-effective because of the expense of the test itself.

### Treatment of established infection with MRSA

For 20 years, glycopeptides have become the mainstay of treatment in the United Kingdom. Vancomycin and teicoplanin have become the drugs of choice.\(^\text{70}\) Both are given parenterally, although vancomycin is less well tolerated and the penetration of teicoplanin into bone is better than that of vancomycin.\(^\text{71}\) Although teicoplanin can be administered as a bolus dose and can therefore be given on an outpatient basis,\(^\text{51}\) in the United Kingdom both antibiotics are generally regarded as suitable for inpatient treatment.

MRSA is no longer exclusively regarded as a nosocomial infection. Although most community-associated strains\(^\text{16}\) are only β-lactam resistant, staphylococcal resistance to glycopeptides has been reported.\(^\text{72}\) There are also concerns about strains of *Staph. aureus* with reduced sensitivity to vancomycin and their emergence in the community.\(^\text{73-75}\)
A most important development in the pharmacotherapy of infection with MRSA has been the discovery in the late 1980s of the oxazolidinones. These antimicrobials inhibit an early step in protein synthesis. Linezolid was the first in this class of antibiotic to be licensed and has excellent tissue penetration with 100% bioavailability. The successful use of linezolid compared with vancomycin, specifically against MRSA, has been documented in a large randomised trial. It has also been shown to be effective in a smaller, non-randomised trial in which vancomycin had previously failed against predominantly MRSA osteomyelitis. Linezolid is recommended as an alternative when conventional therapy has failed or is not tolerated. It allows oral, and hence outpatient, administration. However, the apparent increase in side-effects, particularly the bone-marrow suppression seen on prolonged administration, means that it should only be used under careful surveillance until its complications are better understood. Larger controlled studies should be undertaken before it is given widespread, prolonged use.

**Recommendations for the future**

The spread of MRSA, and in particular its increase as a community-associated pathogen, should be of great concern to the clinician. As most risk factors for the development of infection with MRSA are predetermined on admission to hospital, we feel that the focus must be on adequate prophylaxis and the early identification and treatment of affected carriers.

Although there are guidelines to prevent the spread of MRSA, these have had little or no effect on the overall rates of infection in the United Kingdom. This may be because of poor compliance but some believe that the number of cases has exceeded the resources available to achieve control. More recent suggestions have focused on surveillance cultures, followed by the eradication of MRSA when it has been detected. As shown by the SENTRY study, several northern European and Scandinavian countries have very low rates of infection with MRSA as compared with the United Kingdom. In The Netherlands, where rates are <1%, a search-and-destroy policy has been adopted. This entails the isolation and screening of patients deemed to be at risk of infection before their admission to hospital. They are only admitted when negative swabs have been obtained. It is felt that this policy, combined with the restrictive use of antibiotics, is responsible for such low rates in The Netherlands.

A similar isolation policy, combined with strict control of infection has given good results in an orthopaedic unit in the United Kingdom. Other studies in the United States have shown surveillance cultures and enteral vancomycin to be safe and effective methods of controlling MRSA.

From the perspective of orthopaedics and trauma, Table III gives a suitable protocol. In practice, however, clinicians and infection control specialists should agree on the measures which are necessary and feasible locally. Compliance with agreed policies must be monitored and clinical audit should be encouraged in order to review the effectiveness of local protocols.

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