What is the size and nature of the current need for single room isolation in hospital, and how does success or 'failure to isolate' patients affect the control of meticillin-resistant *Staphylococcus aureus* (MRSA)?

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Submitted in accordance with the requirements for the degree of PhD.

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August 2007

Acknowledgements

I would like to thank the following people, groups and organisations for their support in completing this work.

Professor Mark H Wilcox for supervision, support and advice throughout the research

The Microbiology and Infection Control Team – The Leeds Teaching Hospitals NHS Trust for support and cooperation with data collection

Peter Parnell, Paul Verity, Dr Warren Fawley and colleagues in the Infection Control Laboratory, The Leeds Teaching Hospitals NHS Trust, for training, supervision and support in laboratory techniques

The staff of the wards and departments of the Leeds General Infirmary for cooperation with data collection

For support and funding:

NHS Estates & The Department of Health (England)

The Health Foundation (formerly the PPP foundation)

Abstract

Healthcare-associated infections, in particular those caused by antibiotic-resistant organisms, are a major cause of morbidity, mortality and increased cost to healthcare providers and MRSA are, in terms of prevalence, by far the most significant resistant organisms in the United Kingdom as well as many other countries worldwide.

Isolation of hospital patients, usually in single rooms, is intended to interrupt the transmission of potential pathogens between patients and/or staff. Risk assessment is used to determine whether individual patients with potentially transmissible pathogens, including MRSA, should be isolated in single rooms. However, limited isolation room availability and/or operational needs may compromise this process and this has contributed to a general perception that although isolation may be recommended, in many cases it is not achieved due to a lack of facilities and conflicting priorities for the use of those facilities.

Despite it being considered as standard practice the evidence for the efficacy of isolation in a single room in preventing the transmission of MRSA is limited.

An initial study examined, prospectively, the incidence of isolation failure in a large UK National Health Service hospital and the relationship between the rate of 'failure to isolate' of patients from whose clinical samples MRSA had

been identified and the rate of MRSA identified from samples sent for clinical purposes, per ward. A subsequent study compared the transmission of MRSA from index cases who were isolated and those who were not isolated with a cohort of contacts who were immediately adjacent to them.

The results of these studies demonstrate that 'failure to isolate' is a frequent occurrence; isolation requirements were not met in 22% of cases and that there was a significant correlation between failing to isolate patients with MRSA, and rates of MRSA identified from samples sent for clinical purposes (Spearman's $\rho = 0.596$, $p < 0.001$). Conversely there was no significant difference in the MRSA acquisition rates in the contacts of people with MRSA who were not isolated *vs.* index cases who were isolated. Risk factors for MRSA acquisition in multivariate analysis were: exposure to antibiotics (quinolones and macrolides), presence of a nasogastric tube, dermatological conditions and the index case being risk-assessed as requiring isolation. Further research is needed into the efficacy of isolation in preventing the hospital transmission of MRSA.

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1. Introduction

1.1. Healthcare-associated infection

Healthcare-associated infection (HCAI) has replaced the traditional term 'hospital-acquired infection' (HAI) because of the increasing delivery of healthcare in settings other than hospitals *e.g.* general practitioners' surgeries and in people's own homes. The term can be used to describe any infection acquired through exposure to any health intervention such as surgery, medical treatment or care activities *e.g.* nursing or physiotherapy.

The overall prevalence of HCAI has not been measured due to the complex nature of healthcare delivery; however, there are a number of studies that have reported the prevalence and incidence of HAI. In the developed world the reported prevalence of all HAIs is in the range of five to ten percent. [1] Preliminary results of the United Kingdom (UK) third National Prevalence Survey of Healthcare-Associated Infections in Acute Hospitals conducted in 2006 give the overall rate of HAI in acute hospitals in England as 8.19% (95% confidence intervals 7.97 – 8.41%).[2] This figure is little changed from that of 9% found in the second National Prevalence Survey ten years earlier; [3] however any comparisons between the two studies can only be made with extreme caution as the methodologies employed, including the definitions of infection, were different.

The overall impact of HAI on morbidity and mortality is unknown but it has been estimated that around 5,000 deaths a year in the UK may be

attributable to HAI and that HAI may contribute substantially to a further 15,000.[4] The economic impact of HAI has been studied by Plowman and colleagues who, through extrapolation from one district general hospital, estimated the cost of HAI in England to be ~£930 million per annum (hospital costs only).[5] The authors recognise that this figure is a relatively crude estimate due to the difficulties in such extrapolation and, additionally, this study excluded day-case activity, which is becoming greater over time, though only slowly; [6] nevertheless it gives an indication of the burden of HAI on National Health Service (NHS) finances.

1.2. Healthcare-associated infections caused by antimicrobial resistant organisms

Organisms that are resistant to antimicrobial agents present a significant threat to public health.[7] In particular, the emergence of multiply antibiotic-resistant bacteria as significant nosocomial pathogens is a major threat to the safe and successful provision of healthcare. Members of a number of bacterial genera that cause HCAI exhibit resistance to antibiotics including: multiply-resistant staphylococci, glycopeptide-resistant enterococci and multiply-resistant Gram negative bacilli including those that produce extended-spectrum β-lactamases (ESBLs).

Although there are data to indicate increasing resistance in a number of species including; *Enterococcus faecium*, *Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *and Acinetobacter* spp.: the most significant

multiply-resistant bacteria, in terms of both prevalence and impact, are meticillin-resistant *Staphylococcus aureus*. [8 9]

1.3. Staphylococcus aureus and meticillin-resistant Staphylococcus aureus (MRSA)

1.3.1. *Staphylococcus aureus*

Staphylococcus aureus is a ubiquitous, opportunistic, Gram-positive, coagulase-positive bacterium that colonises up to fifty five percent of healthy adults [10 11] with colonisation rates that are twenty five to fifty percent higher in certain groups of hospital patients and staff. [12]

S. aureus can be isolated from a number of body sites including the axilla, perineum and areas of damaged skin but is most commonly found in the anterior nares and elimination from the nose leads to its subsequent disappearance from other body sites. [10] In addition to colonisation, *S. aureus* causes a range of infections from simple skin lesions through the whole range of community- and healthcare-associated infections to life-threatening pneumonia and septicaemia. *S. aureus*, with or without resistance to meticillin, are among the commonest organisms found in a range of HCAI, in particular surgical-site infection [13] and vascular catheter-related bloodstream infection. [14] In addition to opportunistic infections and HCAI, some strains of *S. aureus* are the cause of specific toxin mediated disease such as staphylococcal food poisoning, blistering skin disease, including scalded skin syndrome, and toxic shock syndrome.

1.3.2. Antibiotic resistance in *S. aureus*

S. aureus exhibits no natural antibiotic resistance but strains have acquired resistance to many agents as they have been developed and used in clinical practice. Less than five years after the earliest use of penicillin, resistance to this drug through production of penicillinase (a β-lactamase) was, by 1946, already found in 6% of *S. aureus* clinical isolates; this figure growing to over 50% by 1948.[15] Currently, more than 90% of *S. aureus* are resistant to penicillin. [9] Livermore summarises the rapid emergence of resistance in *S. aureus* to other natural antibiotics, including chloramphenicol, erythromycin, streptomycin and tetracycline, all of which were rendered ineffective against particular strains before the 1960s.[16]

The penicillinase-stable β-lactam antibiotics were developed in the early 1960s, these included methicillin (now meticillin), nafcillin and flucloxacillin. Resistance to these agents, and thus the emergence of MRSA, occurred very quickly, with meticillin resistance being reported within a year of the drug becoming commercially available. [17] This bears a remarkable historical similarity to the first report of resistance to penicillin in *S. aureus* which was also within one year of its first use. [18]

Strains of *S. aureus* acquire meticillin resistance through chromosomal incorporation of the *mecA* gene. The *mecA* gene is incorporated within the Staphylococcal Chromosomal Cassette, SCC*mec*, a large, mobile genetic element that is known to occur in five types ranging in size from 20 to 67 kb;

mecA encodes PBP2', an additional penicillin binding protein in the cell wall of MRSA. This effectively prevents penicillinase-stable β-lactam antibiotics acting by providing an additional penicillin binding protein that has reduced affinity for, and thereby reduced binding to, β-lactam drugs, thus permitting synthesis of peptidoglycan.[19] In addition to the penicillinase-stable penicillins this mechanism confers resistance to all β-lactam antibiotics including cephalosporins and carbapenems. Resistance to other families of antibiotic varies with different isolates and is dependent on which other antibiotic resistance genes have been acquired and are carried by the resistant strain. A recent survey of UK microbiology laboratories identified that 92% of MRSA strains were resistant to quinolones and 72% to macrolides.[20]

Once it had emerged, meticillin resistance spread rapidly, Grundmann *et al.* summarise the situation by 1967 when MRSA had been reported from four countries in Europe including England,[21] where in one large general hospital MRSA accounted for almost 10% of all *S. aureus* isolates.[22] At that time, MRSA were reported from India and Australia as well as from Europe. However, the incidence in Europe then declined during the 1970s, falling close to nil by the early 1980s.[16] Ayliffe suggests that this decline may have been due to improvements in antibiotic control and infection control during this period.[22]

By the mid 1980s isolates of MRSA were re-emerging. These isolates were characterised by gentamicin resistance. The strain, known in the UK as 'epidemic' or 'EMRSA' 1 was reported from a number of countries including the USA, Republic of Ireland, Australia and the UK. [16 21 23] Epidemic strains of MRSA in the UK were numbered sequentially as they were identified, and are described as those that had spread to two or more patients in two or more hospitals. In the late 1980s EMRSA 3 was common in the UK and by the mid 1990s this strain, along with EMRSA 15 and EMRSA 16, were the principal strains affecting UK hospitals. [24] Recently, a putative EMRSA 17 has been described in the UK with the specific phenotypic characteristic of reduced susceptibility to glycopeptides. [25]

In the UK, and in many parts of southern and central Europe (though not northern Europe) and in other developed countries around the world, the prevalence of MRSA rose dramatically through the 1990s and into the early 2000s. Johnson and colleagues report that during this period the proportion of *S. aureus* bacteraemias reported to the various UK surveillance systems rose from < 2% to around 40%.[26] Through intense public, media and political interest, this rise led to a mandatory surveillance system for MRSA bacteraemia and a mandatory reduction target for NHS Trusts in England. [27] [28] Since the inception of these measures the proportion of *S. aureus* bacteraemias in England that are MRSA has remained stable at around 40%. [29]

Recent work, using multi-locus sequence typing (MLST) and DNA microarray analysis, has established more precisely the worldwide evolution of MRSA. Meticillin resistance had been thought previously to have spread from a single-meticillin resistant strain that evolved from an epidemic strain of meticillin-sensitive *S. aureus* (MSSA); however, MLST studies have concluded that meticillin resistance has been genetically transferred, through horizontal transfer of SCC*mec* to sensitive *S. aureus* on at least five occasions since its emergence. [30]

In recent years a small number of reports have identified strains of MRSA with reduced susceptibility to glycopeptide antibiotics. [31-36] The definitions of reduced susceptibility have been described as confusing by the most recent UK guidance on susceptibility testing in *S. aureus* and the authors recommended the use of the terms: VISA (vancomycin), GISA (glycopeptide) and TISA (teicoplanin) for isolates exhibiting homogenous low-level, intermediate, resistance to these agents and the term VRSA for high-level resistance to vancomycin *i.e.* MIC $\geq$ 32 mg/L.[20] In addition to these reports, others have reported heterogeneous resistance where, despite an MIC within the susceptible range, sub-populations within a strain exhibit reduced susceptibility to vancomycin; the clinical significance of these findings is not clear. [34 37 38] As well as resistance to systemic antibiotics there is evidence of established and increasing resistance to mupirocin, a

topical antibiotic used to eradicate staphylococci from sites of colonisation, particularly the anterior nares. [20]

In recent years, there have been reports of an entirely new development in the epidemiology of MRSA. Historically, the overwhelming majority of cases of MRSA have been attributable to contact with healthcare, usually hospitals, but latterly there have been reports of MRSA infections in healthy adults and children without previous contact with hospitals or healthcare of any description and without any known risk factors for MRSA. [39] These cases have presented as serious skin and soft-tissue infections [40] including necrotising fasciitis [41] and, more rarely, as a necrotising pneumonia. [42] These community-acquired strains of MRSA (CA-MRSA) are distinct from hospital-acquired strains in a number of ways including: increased virulence due to the presence of the Panton-Valentine leukocidin (PVL) and a lack of genes encoding resistance to a range of antibiotics other than those in the β-lactam family.

Research by Robinson *et al.* [43] using MLST has suggested that CA-MRSA strains circulating currently are the re-emergence, with the addition of meticillin resistance, of the notorious strain of MSSA known as 'phage type 80/81 which caused a pandemic of both hospital- and community-acquired infection during the 1950s and 1960s. There have been large numbers of cases of CA-MRSA reported in North America, [40 41 44-51] as well reports from

Europe [52-54] and Australasia, [55 56] however CA-MRSA currently remains rare in England and Wales [57] and it will not be considered further.

1.3.3. Identification and typing of MRSA

UK recommendations for both routine and rapid identification methods for MRSA in both clinical and screening samples, as well as tests for antibiotic susceptibility, have been published recently. [58] Typing techniques for *S aureus* and MRSA can be divided into phenotypic and genotypic techniques. Phenotypic techniques *e.g.* antibiogram comparison and bacteriophage typing, are the traditional methods and are still widely used. Comparisons of antibiotic susceptibility patterns may serve as a useful indicator of relatedness leading to selection of isolates for further typing [24]. Such usefulness, however, is limited as genetically-unrelated isolates may have the same antibiogram [59] and those that are genetically related may have small differences in their antibiogram. [60] Similarly, Bacteriophage typing has been criticised because of the number of isolates that are non-typeable by this technique [59] although this problem can be reduced by such adjuncts as typing at 1000 x RTD, heat treatment at 48° C and 'heat shocking' at 55-56° C. [61 62]

The available molecular or genotypic techniques for *S. aureus* and MRSA typing are Pulsed Field Gel Electrophoresis (PFGE), MLST, SCC*mec* typing and *spa* typing, which is a single locus typing method based on the *S. aureus* Protein A gene (*spa*). PFGE is widely used and is considered the

reference standard for MRSA typing, particularly for local epidemiological investigations; however the need for subjective interpretation makes comparisons between laboratories difficult, although improvements in comparison software have reduced these problems. The technique involves digestion of MRSA chromosomal DNA, typically using the digestion enzyme *Sma*I, and subsequent separation of the digestion fragments by an adapted agarose gel electrophoresis technique. [63-65] The interpretation of the PFGE band patterns to determine if isolates are epidemiologically related has been described by Tenover *et al.* [66]

MLST uses DNA sequence determination of fragments (approximately 500 bp) of seven housekeeping genes, the sequences identified are compared with known allelic profiles and given a sequence type. MLST is considered less discriminatory than PFGE for local epidemiological investigation but has been used successfully to identify the global epidemiology of MRSA. [30 67]

SCC*mec* typing, using polymerase chain reaction (PCR) techniques, identifies the isolates according to which of five currently known SCC*mec* types they carry. This information combined with resistance data (*i.e.* meticillin susceptibility) and MLST type has been proposed as an international standard nomenclature for *S. aureus* including MRSA. [67] Because it involves the sequence determination of only a single locus, *spa*

typing has been proposed as a simple technique that can be used locally, that is discriminatory enough for studies of both molecular evolution and local epidemiological investigations. [59 63]

1.3.4. Treatment of MRSA infection

Guidance on the prophylaxis and treatment of MRSA infections has been published recently. [20] Although treatment choices may be limited, the authors recommend a number of different agents depending on the susceptibility patterns of the MRSA strains encountered; for serious and life-threatening infections, however, the glycopeptide antibiotic vancomycin is recommended, either as sole agent or in combination with rifampicin or fusidic acid. An alternative option to vancomycin and the agent of choice where there is reduced susceptibility to glycopeptides is the relatively recently developed agent linezolid but holding other novel agents such as quinupristin/dalfopristin in reserve has also been recommended.

1.3.5. Epidemiology of MRSA colonisation and infection

1.3.5.1. Risk factors for MRSA colonisation and infection

MRSA carriage in the general population, outside of nursing homes, hospitals and other care settings, is generally low, whether or not the prevalence in healthcare facilities is low [68] or high. [11 69 70] The epidemiology of the spread of MRSA both within and between healthcare institutions is complex; the emergence of MRSA *de novo* is considered to be a rare event and the majority of cases worldwide are due to the intra- and inter-hospital

spread of a relatively small number of epidemic strains, as described by Robinson and Enright. [67]

A review by Safdar and Maki [71] identified what they describe as "impressive commonality" of risk factors for colonisation and infection with a number of epidemiologically-important bacteria including antibiotic-resistant *S. aureus,* enterococci and Gram-negative bacilli as well as *Clostridium difficile* and *Candida* spp. This suggests that host factors and medical interventions are as at least as important as organism factors in the acquisition and spread of pathogens.

Colonisation frequently precedes infection [10 72 73] and a number of studies have identified putative risk factors for colonisation in a variety of patient populations. Nouwen *et al.* describe the determinants of *S. aureus* nasal carriage and note that host factors including; ethnic groups, gender, age and the presence of underlying diseases affect the likelihood of carriage. [10] Independent risk factors identified using multivariate analysis for MRSA acquisition for in-patients on general wards include: prolonged hospital length-of-stay (LOS),[74 75] pressure sores, [74] physiotherapy, [74] surgical and invasive procedures, [74 75] intensity of care, [76] number of ward transfers, [76] antibiotic therapy, [75-77] underlying illnesses, [75 78] older age, [75 79] previous hospitalisation, [77-80] residence in a nursing home [78-80] and HIV infection. [77] In 2005, Hidron *et al.* also identified a diagnosis of skin or soft-tissue infection

on admission to hospital as an independent risk factor for MRSA colonisation which reflects the emergence of CA-MRSA in North America. [77]

Risk factors identified using multivariate analysis for clinical infection with MRSA are: MRSA colonisation, [73] nursing home care, [81] prior hospitalisation, [81 82] increasing age, [81] intensive care, [83] surgical wounds, [82 83] pressure sores, [83] intravenous catheterisation, [83] increased LOS, [82 84] antibiotic therapy, [82 84] enteral feeding. [82] In surgical patients specifically, risk factors include: gastrointestinal malignancy, sepsis, [85] discharge to long-term care (which may be a surrogate for admission from long-term care) and duration of post-operative antibiotic therapy. [86] The presence of a nasogastric tube has been identified as a risk factor for MRSA acquisition and infection but only in univariate analysis. [83 87 88]

A number of studies have examined the risk factors for MRSA bacteraemia; most have used MSSA bacteraemia as the comparator and the methodologies used included both prospective and retrospective data collection. The risk factors identified were similar to those above; intravascular catheterisation, [89-91] recent previous hospitalisation, [92 93] 'assisted living', [92 93] critical care, [90] urinary catheterisation, [91] infection at the surgical site, [91] older age and underlying illness. [94]

Risk factors for colonisation and infection have also been identified in specific patient populations; in intensive care patients the following factors have been identified: colonisation pressure (the presence of other MRSA colonised patients),[95] [96] increased LOS,[97] [98] history of hospitalisation,[97] surgery,[97] [98] skin lesions (including pressure sores),[97] [99] antibiotic therapy,[96] [98] central venous catheterisation,[96] tracheostomy and enteral nutrition.[99]

Other patient groups studied include in-patients infected with HIV in whom prior hospitalisation, antibiotic therapy, invasive procedures and cannulae, dermatological conditions and a low CD4 count were independently associated either with colonisation or infection with MRSA,[100] [101] elderly-care populations (who require assisted living, or have antibiotic exposure or recent hospitalisation)[102] [103] and infants in a well-infant nursery in whom circumcision and the use of lignocaine injections were identified as being associated with MRSA colonisation.[104] This latter study and a study by Skiest *et al.*[105] of MRSA *vs.* meticillin-susceptible *S. aureus* (MSSA) infections, in which risk factors for MRSA included ethnicity (African-American) and homelessness, again reflect the changing epidemiology of MRSA infection in places, such as the United States of America (USA) where community-acquired strains of MRSA have become a prominent cause of clinical infection.

Other studies have identified organisational factors that may affect the incidence of MRSA. Vicca [106] describes a significant temporal relationship between peaks of nursing staff workload and an increased number of MRSA cases. The correlation (Pearson's $\rho = 0.1146$; $p < 0.001$) may reflect the complexity of MRSA transmission in which nurse-patient ratio may only be a small contributing factor. This finding is supported by Bignardi & Askew, [107] however their data compare the prevalence of MRSA, and *Clostridium difficile*, with finished consultant episodes rather than direct nurse-patient ratios and could simply reflect increased overall activity rather than relative increases in workload. Blatnik & Lesnicar [108] measured MRSA transmission and the workload of nursing staff prospectively in an intensive care unit using a recognised workload scale, over a two-year period. They demonstrated a convincing correlation between increased workload and increased MRSA transmission ($p < 0.001$; F test). This finding is supported indirectly by the work of Huggonet *et al.* [109] who, in a prospective cohort study of nearly 2000 ICU patients, found that a higher 24-hour nurse-patient ratio was significantly associated with a lower incidence of all nosocomial infections.

Mathematical modelling of MRSA transmission in ICUs has produced conflicting data on the impact of staffing levels, with one model identifying relative staff deficit as significantly associated with transmission (adjusted rate ratio for transmission 1.05, 95% CI 1.02 to 1.09)[110] and another similar report finding that the impact of increasing staffing, unless combined with strict staff-patient cohorting, could actually increase transmission. [111] It has

been proposed that reduced staffing leads to reduced patient contact as only essential tasks are undertaken, thus leading to fewer opportunities for cross infection. [112] Because of the nature of critical care nursing, *i.e.* one-to-one care being the norm, it is unclear as to whether these findings could be generalised to other care settings.

Borg [113] describes a significant correlation between bed occupancy and numbers of MRSA cases over two years ($r = 0.463$; $p < 0.05$) and describes an anecdotal use of extra beds with smaller bed spaces at times of peak occupancy. A causal relationship is implied; however the data could be interpreted alternatively as increased numbers of cases of MRSA leading to higher bed occupancy or as both higher bed occupancy and increased cases being confounded by, for example, the admission of more severely ill patients. A potential relationship between bed occupancy and nosocomial MRSA transmission is, however, plausible and of some concern in the UK where bed occupancy rates average 95%.[114] The hypotheses that increasing the numbers of beds at the expense of the space between them increases the risk of MRSA transmission is supported by the earlier work of Kibbler *et al.*, [115] who found that the relative risk of colonisation with MRSA through adding an extra bed to four bedded bays was 3.15 ($p < 0.005$; χ^2). Cunningham *et al.* [116] used national data for Northern Ireland to identify a significant correlation between MRSA infection rates and both bed occupancy and bed turnover interval, the latter association being the stronger of the two.

1.3.5.2. Exposure to antibiotics as a risk factor for MRSA colonisation and infection.

As previously noted, meticillin resistance in *S. aureus* is rarely the result of *de novo* bacterial mutation in response to the presence of antibiotics; however many studies have highlighted the link between prescription of antibiotics and MRSA, as both a risk factor for individual patients and a driver for increasing prevalence in healthcare facilities. It is also true that, in Europe, on the whole, those countries with the lowest rates of MRSA infection also have low rates of antibiotic prescribing, although the UK, which has relatively high rates of MRSA infection has rates of prescribing that are almost as low as in Scandinavia and the Netherlands: areas with a notably low number of MRSA infections. [117-119]

A number of classes of antibiotic have been implicated as risk factors for MRSA colonisation and infection including macrolides, [82 85 100 120] (all) β-lactams, [89 100 120-122] aminoglycosides, [85 89 100 120] clindamycin, [100] carbapenems, [85 100] aztreonam [100] and tetracycline. [85] The classes that have shown the most consistent association with MRSA incidence, however, are the cephalosporins (in particular, the third-generation agents) and the quinolones. Fukatsu *et al.* [123] identified a significant temporal correlation between prescriptions of third-generation cephalosporins and MRSA surgical site infections ($p < 0.01$; χ^2) however the study was retrospective and longitudinal and no attempt was made to assess the impact of other factors on MRSA incidence. Hill *et al.* [124] in a small case-control study identified a

significant risk for MRSA acquisition associated with administration of a cephalosporin ($p = 0.04$; Fisher's exact test). The authors give limited information about the study and it is possible that the study was insufficiently powerful to identify a significant difference between cases and controls in other risk factors for MRSA. For example, there was a difference in the proportion of patients with urinary catheters (65% in cases *vs.* 41% in controls) but, in this small sample, this was not statistically significant.

In a seven-year hospital wide study, Donegan *et al.* [121] identified a significant correlation between prescriptions of third-generation cephalosporins and the incidence of nosocomial MRSA bacteraemia. Again, there is no assessment of other factors that may have had an impact on MRSA bacteraemias over this period.

In a large multi-centre study, Crowcroft *et al.* [122] used multivariate analysis to identify a highly significant correlation between use of the third-generation cephalosporins; ceftazidime and cefsulodin and nosocomial MRSA (regression coefficient 0.38; $p = 0.0003$). The same study also identified a significant correlation with the use of quinolones (regression coefficient 0.36; $p = 0.05$). Quinolones were also implicated in the study by Hill *et al.* described above but the risk was not significant ($p = 0.16$; Fisher's exact test); however this may be again be due to the small sample size and consequent lack of statistical power. Chiang *et al.* [125], in a case-control

study, identified levofloxacin use as an independent predictor of nosocomial MRSA infection (OR 2.8), the authors give limited information about their methods so the reliability of these data is difficult to assess. Dziekan *et al.* [76] in a case-control study and using multivariate analysis found that quinolone therapy was a significant independent risk factor for nosocomial MRSA ($p = 0.025$, conditional logistic regression).

In a *post-hoc* evaluation of a study designed to evaluate the effectiveness of nasal mupirocin in eradicating MRSA, previous receipt of a quinolone was an independent risk factor for persistent carriage of MRSA. [126] A case control study by Graffunder and Venezia [82] using logistic regression analysis again identified, levofloxacin, both in absolute terms ($p < 0.001$; χ^2 of the likelihood ratio) and in terms of the number of grams administered ($p = 0.003$; χ^2 of the likelihood ratio), as independently associated with risk of MRSA infection *vs.* MSSA infection. The use of patients with MSSA bacteraemia as controls instead of patients with no disease has been criticised as having the potential to overestimate the association between antibiotic use and MRSA acquisition. [127]

Muller *et al.* [120] used an ecological approach to study the relationship between antimicrobial use and MRSA acquisition by 'unit' (wards and departments). Multivariate analysis showed a significant independent association with MRSA acquisition for all classes of antibiotics studied,

including quinolones and cephalosporins (p for both < 0.01; χ^2 of the likelihood ratio). The authors also noted that only these two classes of antibiotics exhibited a linear dose-effect relationship between usage and MRSA incidence.

The study by LeBlanc *et al.* [128] identified, through retrospective review of hospital records, the risk of healthcare-associated MRSA colonisation and infection related to previous administration of antimicrobial drugs. The authors found that, of the antimicrobials studied and, after adjustment using regression analysis, only quinolones increased the risk of colonisation and infection (p for both < 0.05; Cox regression analyis).

Two studies have been specifically designed to examine the hypothesis that quinolones increase the risk of MRSA colonisation and/or infection. Weber *et al.* [129] used a case–case–control group methodology (essentially, two parallel case-control studies) as a more robust method of determining risk in studies of antimicrobial resistance. The results of their multivariate analysis results show both ciprofloxacin ($p < 0.0001$; χ^2 of the likelihood ratio) and levofloxacin ($p = 0.005$; χ^2 of the likelihood ratio) as independent risk factors for nosocomial MRSA acquisition but not for nosocomial MSSA acquisition.

Bosso and Mauldin [130] used an interrupted time-series study to assess the impact of the introduction of levofloxacin and its subsequent replacement

with gatifloxacin in a hospital formulary on nosocomial MRSA infection rates. Their results appear to show an association with an accelerated increase in MRSA infection rates with levofloxacin but a reversal of this trend with gatifloxacin. The authors recognize that other factors (such as infection control precautions) may have impacted on MRSA infection rates over the study period, but the claim that gatifloxacin reversed the trend for increasing MRSA infection needs to be interpreted with caution; with the exception of a single data point, which could be explained by a cluster of MRSA transmission, the MRSA infection rates during the levofloxacin period lay within the same range as during the post-levofloxacin (gatifloxacin) period.

A number of studies have proposed mechanisms for the increased risk of MRSA acquisition associated with quinolones, in particular ciprofloxacin. Bisognano *et al.* have identified that exposure of both meticillin-sensitive and resistant *S. aureus* to sub-inhibitory levels of ciprofloxacin promotes the expression of fibronectin-binding proteins which are involved in bacterial adhesion. [131] [132] Such exposure to sub-inhibitory levels of ciprofloxacin *in vivo* may occur through the excretion of the agent in sweat; exposure of this nature has been demonstrated in other staphylococci. [133]

An *in vitro* study by Venezia *et al.* [134] demonstrated an increase in high-level oxacillin-resistant strains in a heteroresistant population of *S. aureus* in the

presence of quinolones, thus potentially increasing the risk of colonisation by these strains. This has yet to be supported by further studies.

The identification of risk factors for MRSA acquisition is complex and the potential for confounding high; the number of putative risk factors identified in the literature makes it certain that no study has identified and controlled for all the possible risk factors; in particular studies that have not controlled for exposure to antibiotics need to be treated with caution as there is a strong and consistent association between such exposure and MRSA acquisition.

1.3.6. The clinical and economic impact of MRSA

Although most patients are colonised rather than infected with MRSA there is considerable evidence to support the hypothesis that MRSA cause increased morbidity and mortality when compared with MSSA. Two studies have identified an increased risk of clinical infection related to MRSA nasal colonisation; Pujol *et al.* [72] demonstrated a relative risk (RR) of developing bacteraemia of 3.9 comparing MRSA nasal carriers to MSSA nasal carriers ($p = 0.002$; Cox proportional-hazards regression), Davis *et al.* [73] showed a similar increased risk of MRSA infection whether the MRSA nasal colonisation was present on admission (RR 13, 95% confidence intervals [CI] 2.7 to 6.4) or acquired (RR 12; 95% CI 4 to 38).

The impact of MRSA on mortality has been described by a number of studies. Two systematic reviews with meta-analysis comparing mortality in MRSA *vs.* MSSA bacteraemia have been published. Whitby *et al.* [135] analysed nine studies, published between 1978 and 2000, of which eight found an increased mortality from MRSA bacteraemia. The combined relative risk for mortality was 2.12 (95% CI 1.76 to 2.57).

The meta-analysis published by Cosgrove *et al.* [136] covered a similar period but identified and included 31 studies. Again, there was a significant increase in the risk of death from MRSA *vs.* MSSA bacteraemia (odds ratio = 1.93, 95% CI 1.54 to 2.42). This latter review noted that there was significant heterogeneity between the included studies which was at odds with the findings of Whitby and colleagues; this difference may be explained by the larger number of studies included in the analysis of Cosgrove *et al.*

Chang *et al.* [137] conducted a prospective study of 505 consecutive patients with *S. aureus* bacteraemia, they found that although MRSA was a risk factor for persistent bacteraemia it was not a significant risk factor for endocarditis or, when adjusted for other risk factors using logistic regression, mortality, although the trend was not significant ($p = 0.64$; χ^2 of the likelihood ratio), which may suggest an underpowered study for this outcome.

Melzer *et al.* [138] investigated 815 patients with nosocomial *S. aureus* bacteraemia prospectively over five-year period. The adjusted risk of mortality from MRSA *vs.* MSSA bacteraemia was not significant; however no power calculation is presented and the results may be due to an inadequately powered study (adjusted OR 1.72, 95% CI 0.92 to 3.2). Bader [93] studied seven-day mortality in older patients (age ≥ 60 years). Again, after controlling for co-morbidities and disease severity, MRSA was not an independent risk factor; it is not possible to assess the impact of sample size, which was small (n = 135), as adjusted odds ratios and confidence intervals are not given for these findings, which were not statistically significant. Shurland *et al.* [94] conducted a retrospective study of 438 patients with *S. aureus* bacteraemia, they found, after adjustment for co-morbidities and age, significantly higher mortality in MRSA *vs.* MSSA bacteraemia (hazard ratio 1.8, 95% CI 1.2 to 3). Crowcroft and Catchpole [139] analysed data from death certificates in England & Wales over a five year period; the proportion of certificates that mentioned staphylococcal infection and also mentioned MRSA increased from 8% to 44%. The authors admit that this analysis is necessarily crude, as it depends on the quality of reporting, but they conclude that the data do reflect a genuine increase in mortality attributable to MRSA over the period in question.

Possible explanations for the increased risk of mortality associated with MRSA infection include the finding, in many of the quoted studies, that

patients with MRSA infection have more severe underlying disease. However, in a number of studies and in the analysis by Cosgrove and colleagues, who calculated the odds ratio for MRSA *vs*. MSSA mortality in those published studies that controlled for co-morbidity, the risk of death remained significant after adjustment (OR 1.88, 95% CI 1.33 to 2.69). This suggests that, although co-morbidity may modify the risk of death, it does not entirely explain it.

Schramm *et al.* [140] and Lodise *et al.* [141] identify another potential influence on mortality related to MRSA: delayed appropriate antimicrobial therapy. Both studies demonstrate that MRSA is associated with a delay in initiating appropriate antimicrobial therapy and that such delays may be associated with increased morbidity and mortality. In addition, vancomycin may be a less effective anti-staphylococcal agent than flucloxacillin in susceptible strains, making meticillin resistance a driver for increased morbidity and mortality but this is not absolutely proven. [142] [143]

The economic costs of MRSA infection have been reviewed by Gould [144] in 2006 who criticises the fact that many studies examining the costs of MRSA infection report excess costs *vs*. MSSA infection, whereas Gould contends that MRSA infections are an additional burden rather than simply a replacement for MSSA infection. In this review the range of additional costs per case of MRSA infection is quite wide as it includes studies from different

countries and different clinical settings over a period of approximately ten years. Excess costs (all US$) when compared with MSSA ranged from $2,500 to $13,900 and when compared with uninfected controls from $9,275 to $88,445. National excess hospital costs for the USA are estimated at between $1.5 billion and $4.2 billion.

Studies published after the review by Gould have supported the findings in his review. Lodise & McKinnon [145] examined retrospectively 415 cases of *S. aureus* bacteraemia and found that patients with MRSA incurred average excess costs (compared with MSSA) of $9,909. Gavalda *et al.* [146], again retrospectively, looked at all MRSA infections and using only an average cost per patient day for either intensive care unit (ICU) or general ward stays, estimated the average cost per MRSA infection to be €2,730 (*circa* $3,744, based on $1 = ~€0.7).

Two studies have examined costs associated with specific patient populations; Greiner *et al.* [147] compared MRSA with MSSA bacteraemia in haemodialysis patients. They found that MRSA bacteraemia costs were more than double those of MSSA, €24,931 ($34,220) *vs.* €10,573 ($14,515). Four hundred and ninety nine ICU patients with early-onset ventilator-associated pneumonia (VAP) were studied retrospectively using a USA multi-hospital database by Shorr *et al.* [148]; patients whose VAP was caused by MRSA had excess costs (*vs.* MSSA) on average of $7731.

The nature of the costs described can be summarised as those that arise because of increased length of stay ('hotel costs') and the excess costs of diagnosis, management and treatment such as the costs of antibiotics effective against MRSA, barrier precautions and additional tests and invasive procedures. In addition to these there are the increasing costs of litigation and the opportunity costs of cancelled procedures due to ward closure.

1.3.7. MRSA transmission in healthcare settings

Epidemic strains of MRSA have demonstrated a remarkable ability to spread both within and between healthcare settings. The main reservoir of MRSA within healthcare settings is colonised or infected patients and the primary route of transmission of MRSA within healthcare settings is considered to be via the hands of healthcare workers, with or without contact with the inanimate environment or fomites. [149] [150] McBryde *et al.* [151] found that 17% of contacts between a healthcare worker (who had touched the patient, bed or bedclothes) and a patient colonised with MRSA resulted in transmission of MRSA to the gloves of the healthcare worker. Furthermore, in cases where healthcare workers did not don gloves, MRSA was recoverable from their hands, after hand washing, in two out of five cases where MRSA was isolated pre-hand wash.

A prospective study of the acquisition of MSSA compared with historical data for MRSA by Vriens *et al.* [152] supported the theory that MRSA spreads more

readily than MSSA; the authors suggested that this potential for spread was related to either antibiotic selection pressure or to some factor, as yet unidentified, intrinsic to MRSA. The contribution of antibiotic selection pressure as a significant factor is supported by the studies described in section 1.3.5.2 that identified antibiotic use as a significant risk factor for the acquisition of MRSA, in particular the work of Weber and colleagues in which MSSA acquisition, unlike MRSA, was not related to exposure to quinolones. [129]

Simplistically, at any given time the prevalence of MRSA in a healthcare setting will be the sum of those patients who were colonised on admission added to those who have acquired MRSA in that setting (transmission), less those colonised patients who are 'removed' *i.e.* decolonised, discharged or died . This dynamic has been studied using mathematical modelling techniques that allow for stochastic influences. Three studies have been set in intensive care units: Grundmann *et al.* [110] calculated that, in the absence of any infection-control procedures, each index case of MRSA could generate as many as ten secondary cases through transmission, but with hand hygiene compliance at 59% and cohorting of contacts at 65% (taken from observations in their own unit) this figure would be reduced to 1.52. Cohorting appears to be defined, in this case, as limiting those staff caring for MRSA positive patients to those patients only during a span of duty; however the authors fail to define this precisely. A similar study by Forrester

& Pettitt [153] modelled rates of transmission of MRSA to susceptible patients per day from three potential reservoirs; Patients with MRSA nursed in isolation, MRSA patients not in isolation and 'background sources' – defined as nosocomial transmission outside of the ICU or from undetected MRSA cases within the ICU. Their calculations suggest that background transmission occurs more frequently than transmission from known cases, whether isolated or not; approximately one transmission every 109, 667, and 192 patient days, respectively. This comparison should be interpreted with caution as the denominators for each category are different; per patient day, per day – per patient who was not isolated and per day – per isolated patient, respectively. In addition the 95% confidence intervals for all these data are wide. The modelling of McBryde *et al.* [111] supports the theory that, in the intensive care unit, MRSA prevalence is maintained through the repeated admission of colonised patients and they calculated a transmission rate similar to that of Forrester and Pettitt; one transmission per 160 (95% CI; 130 to 210) patient days (for patients not already colonised with MRSA).

Intensive care units are highly specialised environments with high healthcare-worker to patient ratios and it is unlikely that these models would fully explain transmission in general ward settings. Raboud *et al.* [154] modelled MRSA transmission in a general medical ward and calculated a baseline transmission rate approximately tenfold lower than those calculated by the ICU models *i.e.* 0.89 (95% CI; 0.73 to 1.09) transmissions per 1000

patient days or approximately one transmission every 1124 (95% CI; 917 to 1370) patient days.

All models are based on assumptions that may or may not reflect the reality in healthcare settings *e.g.* that a healthcare worker remains contaminated with MRSA until (and only until) they next cleanse their hands, [110 111] or that patients are homogenous with regard to risk factors for MRSA acquisition. [153] Nevertheless such modelling may prompt further research to investigate the effects of interventions that it suggests will be potentially effective.

Transmission by the airborne route has been proposed as a contributing factor to the spread of MRSA. A number of studies have demonstrated that the presence of a viral infection or an allergic rhinitis increases the airborne dispersal of *S. aureus*, [155-157] however these studies looked at MSSA and do not necessarily explain the apparent increased propensity for spread exhibited by MRSA. Two studies by Shiomori and colleagues [158 159] examined airborne transmission of MRSA and found that MRSA carrying particles could be recovered from air samples in the rooms of both colonised and infected patients. The airborne contamination was significantly increased during and immediately after bed-making, it is unclear as to contribution of these findings to the transmission of MRSA between patients as the sampler used was placed only 1 metre from the patients' beds and

though plausible, no assessment was made of the likelihood of this contamination contributing to cross-infection.

Kuramoto-Chikamatsu *et al.* [160] have proposed a novel route for the transmission of MRSA; via healthcare workers touching both their own and their patients' faces. The authors compared the diversity of MRSA genotypes by PFGE in clinical areas and found that the fewest types were present in areas that they suggested had the higher frequency of face touching activity. While an interesting addition to the debate, this single and methodologically-weak study would need significant corroboration before this could be considered a likely route of transmission.

The contribution of environmental and equipment contamination to the spread of MRSA is a matter of some debate. [161-163] That MRSA can persist in the inanimate environment is clear; a review of the literature by Kramer *et al.* found that MRSA survives for between seven days and seven months on inanimate objects. [164] It may not, however, persist in the environment any more than sensitive strains of *S. aureus*, [165] and its ability to persist may be strain dependent. [166]

A systematic review by Griffiths and colleagues [167] identified twenty studies published between 1975 and 2000 that were considered rigorous enough to establish that MRSA contaminates the inanimate care environment and

equipment but only three studies that were able to link the strains in the environment to colonised or infected patients. A second review [168] covering the period 1996 to 2004 and focussing on the impact of environmental cleaning on MRSA control found only four studies that met their inclusion criteria. From these studies they concluded that environmental cleaning does contribute to MRSA control, from which it can be inferred that environmental contamination does contribute to the transmission of the organism in clinical practice, presumably via the hands of healthcare workers and patients.

Studies published more recently reinforce these findings, Oie *et al.* [169] investigated environmental contamination with MRSA and MSSA in a dermatology ward and found high levels of contamination on surfaces that come into contact with multiple patients and noted that certain porous materials could not be adequately decontaminated between patients. The authors did not attempt to link contamination to cross-infection directly but highlighted devices used on multiple patients as possible reservoirs of *S. aureus*.

Sexton *et al.* [170] conducted a small, prospective study of MRSA contamination in isolation rooms containing patients carrying MRSA. In 35% of the rooms, MRSA isolated from environmental sites were indistinguishable (using PFGE) from the strains isolated from the patient. This is almost identical to the findings of a study in an intensive care unit by Hardy *et al.* [171]

This study, over a period of 14 months, found strains from patients and their immediate environments that were indistinguishable in 35.7% of occasions. These studies emphasise that the contribution of the environment to cross-infection remains unclear. The magnitude of that contribution has been estimated by an interesting study by Huang *et al.* [172] who, in a retrospective study of nosocomial acquisition of MRSA and VRE, calculated an adjusted odds ratio of 1.4 ($p = 0.04$, using linear regression analysis) for MRSA acquisition in patients who were placed in a room in which the previous occupant had been colonised by MRSA (described by the authors as 'MRSA positive') compared with a previous occupant who did not carry MRSA. However this risk accounted for only 5.1% of all the nosocomial cases of MRSA acquisition during the study, an attributable risk of only 1.1%. This latter finding reinforces the notion that, though the environment may contribute to the transmission of MRSA, direct contact via the hands of healthcare workers remains probably the most important factor.

The contribution of carriage by healthcare workers to the transmission of MRSA is controversial and there are few studies that examined this issue rigorously. Early work by Cookson *et al.* [173] identified three distinct patterns of MRSA carriage; transient carriage, identified at the end of a span of duty but gone on return to duty, short-term carriage; isolation of MRSA only on two consecutive screens, and persistent carriage defined as isolation of MRSA on more than two consecutive screens. Virtually all of the staff

colonisation was explained by close patient contact and, as the staff were caring exclusively for known MRSA patients, there was no opportunity to identify any staff-patient transmission.

There are reports of clusters and outbreaks of MRSA that have been epidemiologically linked to individual healthcare workers with persistent carriage or chronic or recurrent infections, [174-176] but these are rare and most studies describe only the prevalence of MRSA carriage in healthcare workers. Reported prevalence rates range from < 1% to 11% of healthcare workers screened, but comparisons are difficult to make as the prevalence among patients in the hospitals studied varies from rare to endemic. [177-184] A significant criticism of the majority of the published studies in this area is their failure to describe clearly the nature of the carriage that they have identified *i.e.* whether such carriage is transient or more persistent. The most recent UK guidance on the management of MRSA in hospitals recommends that, should staff screening be deemed necessary, great care be taken to distinguish between transient and persistent carriage, noting that the former carries little risk of onward transmission. The guidance suggests that this is best achieved by screening staff before a span of duty. [163] The failure, in the published literature, to consider fully this factor is exemplified by the study published by Blok *et al.* [185] in which the prevalence of MRSA among healthcare workers over a ten-year period was 11%, however staff were screened at the end of their span of duty and after having cared only for

patients colonised or infected by MRSA. Although it is considered to be a rare occurrence Muder and colleagues [186] note that, in the endemic setting, otherwise-healthy staff can present with clinical infections caused by MRSA including skin and eye infections.

1.3.8. Control of MRSA in hospitals

In the UK, guidance on the control of MRSA in hospitals has been published and revised four times since 1986; the most recent guidance in 2005/6 was developed and published under three separate headings, covering; laboratory diagnosis, prophylaxis and treatment and, control and prevention. [20 58 163 187-189] Although there has been an increasing emphasis on risk assessment and the best use of limited resources, the essential strategies recommended for control have remained largely unchanged over this period and reflect guidance published in the USA and elsewhere. [190 191] It is recognised that, in general, there is a paucity of evidence from well-designed experimental or epidemiological studies to support the management of infection control pertaining to MRSA. This point is illustrated by the guidance on control and prevention of MRSA published in 2006; [163] the authors categorise their recommendations using the Centers for Disease Control and Prevention (CDC) classifications [192] based on the strength of the available evidence [see Appendix A]. Of the 57 recommendations (excluding those for strains with reduced susceptibility to glycopeptides) only five are categorised as '1A' (Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiological

studies) and a further 25 as '1B' (Strongly recommended for implementation and strongly supported by certain experimental, clinical or epidemiological studies and a strong theoretical rationale). Almost half of the recommendations are category '2' *i.e.* "Suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale". The main strategies recommended by the guidance for the management of MRSA in healthcare facilities are; surveillance, antibiotic stewardship, screening, topical decolonisation and isolation of cases.

The efficacy of interventions to improve antibiotic-prescribing practices has been systematically reviewed.[193] The authors found that, though some studies have demonstrated clear benefits in strategies aimed at amending or reducing antibiotic prescribing, there are few studies that have included data about the impact on MRSA incidence or prevalence of these strategies. Those studies that did address MRSA showed no significant reduction in MRSA infection rates related to their interventions.

1.3.8.1. Screening for MRSA

Screening of patients and, under certain circumstances, healthcare workers is recommended to identify those not previously known to be colonised with MRSA and guide further management.[163] Although there is a strong theoretical rationale for this approach and screening does undoubtedly identify individuals that clinical samples alone would not,[194-196] the evidence base for the impact of screening on reducing the prevalence of, and

infections by, MRSA is weak. A systematic review by Cooper *et al.* [197] was unable to identify the individual effect of screening as a component of programmes to control and reduce MRSA transmission. Loveday *et al.* [168] also conducted a systematic review and were unable to find any studies in which screening was the primary intervention. Aboelela *et al.* [198] systematically reviewed the literature pertaining to screening for all multidrug-resistant organisms and concluded that the evidence for the role of screening in preventing their transmission is weak. A number of studies have been published after the period included in these systematic reviews (*i.e.* up to June 2005).

In a 19-month prospective cohort study with retrospective controls, Wernitz *et al.* [199] concluded that hospital wide screening of patients with risk factors for MRSA *vs.* no screening reduced the expected rate of hospital-acquired MRSA infection (HA-MRSA-I) by 48%; the expected rate was, however, based on the assumption that there were more patients at high risk of MRSA infection during the screening phase of the study. It is unclear from the study description how this assumption was derived. The actual rather than the expected reduction in HA-MRSA-I was 10 cases or 0.03 cases per 1000 patient days [recalculated from the authors' data].

Shitrit *et al.* [200] conducted a similar prospective intervention study with a retrospective control period but used MRSA bacteraemias as their outcome

measure. They found that screening patients deemed to be at high risk of MRSA colonisation led to a significant reduction in MRSA bacteraemias of 1.8 cases per month (OR 0.56; 95% CI 0.37 to 0.87). The intervention followed a period of unexplained increase in MRSA bacteraemias, including clusters necessitating ward closure, and their findings may be influenced by regression to the mean. In addition there is no comparison of case mix from the control and intervention periods or discussion of possible 'Hawthorne effects' associated with their intervention period. The Hawthorne effect has been described as the problem in field experiments that subjects' knowledge that they are in an experiment modifies their behaviour from what it would have been without such knowledge. [201]

Another similar study was conducted by Clancy *et al.* [202] this prospective study with a retrospective control period examined the impact of screening all ICU patients on both hospital-wide and ICU-specific MRSA infection rates. In this study MRSA infections were reduced from 6.1 to 4.1 per 1000 'census-days' (p = 0.01; paired Student's t test). Infection was defined as the receipt of a clinical specimen and this may have overestimated the number of infections though not necessarily in a biased manner and again, case mix and any potential Hawthorne effect are not discussed.

Other studies that have included increased screening have identified significant reductions in MRSA acquisition and/or infection; however

because of the introduction of multiple interventions simultaneously it is not possible to identify the specific effect, if any, of screening. [203-205] Despite the lack of evidence for its efficacy, there is increasing pressure on hospitals in both the USA and the UK to expand screening programmes for MRSA. This is largely in response to directives from governments, regulators and other authorities. [206 207]

1.3.8.2. The use of topical antimicrobials and antiseptics to treat MRSA colonisation.

Topical agents including mupirocin nasal ointment and skin disinfectants such as chlorhexidine gluconate and triclosan have been used widely in hospitals to attempt temporary or permanent decolonisation of MRSA. The evidence for the efficacy of these agents in eradicating MRSA from sites of colonisation is limited and current UK MRSA control guidelines only recommend their use in outbreaks and in patients due to undergo operative procedures. [163] A Cochrane systematic review, which considered both topical and systemic agents used to eradicate MRSA in carriers, found that the quality of the published studies was low and concluded that there was no evidence to support the use of these agents in clinical practice. [208] This review considered only randomised controlled trials (RCTs) for inclusion and it has been argued that this is too conservative a view of the use of research evidence; [209] nevertheless for intervention studies, where efficacy remains unproven, RCTs should be the methodology of choice.

Evidence published subsequently has been reviewed by Loveday *et al.* [168] who considered one RCT and seven other published studies and also concluded that the evidence does not support the use of systemic or topical antimicrobials for the eradication of MRSA. They noted, however, that the selective use of regimens including nasal mupirocin may reduce the risk of infection in specific patient groups *e.g.* those undergoing orthopaedic implant surgery. [210 211]

The review by Loveday and colleagues included studies published up to June 2004; since then, one RCT and four other trials have been published. In an prospective, uncontrolled trial Kampf & Kramer [212] treated patients up to three times with nasal mupirocin and an antiseptic soap, they claimed eradication rates of up to 94.2%; however, their follow-up period was very short (five days post-treatment) and, despite multiple treatment courses, there was no attempt to identify resistance to mupirocin.

Sandri *et al.* [213] studied the impact of treating nasal carriers of MRSA with nasal mupirocin and chlorhexidine washes on nosocomial MRSA infections in an ICU over a five-year period. They report a year-on-year reduction in MRSA infections which was statistically significant by year five ($p = 0.001$; χ^2). It is unclear whether this reduction can be directly attributed to the use of topical decolonisation as there is no assessment of case-mix or other infection risks in the study population. In addition there is no information

about infection or colonisation rates prior to the intervention so regression to the mean cannot be excluded as a possible explanation for these findings.

Muller *et al.* [214] conducted a retrospective analysis of using, followed by stopping the use of, nasal mupirocin, in consecutive two-year periods in an ICU. They concluded that in the absence of mupirocin, there was a significant increase in endogenously-acquired MRSA ($p = 0.02$; Mann-Whitney test); however their definition of 'endogenously-acquired' is based only on the patient acquiring an infection after having previous nasal colonisation without organism typing. Direct cross-infection leading to exogenous infection could have occurred in some of these cases. As well as suffering from methodological weaknesses, these latter two studies may not be capable of extrapolation beyond the ICU setting.

In a long term, prospective study of a ward with a high proportion of patients at high risk for MRSA colonisation and infection due to repeated hospitalisation and chronic disease, Dupeyron *et al.* [215] measured MRSA nasal carriage and clinical infection during 55 months of nasal mupirocin use. They concluded that a significant reduction in both acquired nasal colonisation and clinical infection ($p = 0.006$ and 0.022; respectively, Student's t test) was attributable to the use of nasal mupirocin; this is a plausible explanation and the authors identified no other changes in patient population or practice during the study period. It is possible that the quality of

infection-control procedures improved over the same period and contributed to the outcome, though improvements in practices such as hand hygiene are notoriously difficult to sustain. [216]

Simor *et al.* [217], in a randomised controlled trial, compared a decolonisation regimen that included nasal mupirocin and chlorhexidine washing with oral rifampicin and doxycycline, with no treatment; 74% of the patients who received the intervention had negative cultures for MRSA at three-month follow-up, compared with 32% of the controls ($p = 0.0001$; χ^2). It is interesting to note that, despite being significantly more effective than no treatment, this very aggressive regimen still failed in 26% of patients. Regimens that include systemic antibiotics are unlikely to be adopted for widespread use in situations where MRSA is endemic because of the fear of increasing antibiotic resistance; however they may be of value in specific high-risk patient populations. [218]

1.4. Isolation precautions to prevent the transmission of potentially infectious microorganisms

Isolation of hospital patients, usually in single rooms, which may or may not have anterooms or controlled airflow, is intended to interrupt the transmission of infectious microorganisms from patient to patient (or staff). The practice of isolation incorporates both the placement of the patient and a group of precautions that are used in addition to standard precautions and are designed to prevent transmission; these are referred to collectively as 'contact' or 'barrier' precautions. Contact precautions encompass: hand

hygiene and the use of protective clothing as well as equipment decontamination and environmental hygiene. Isolation practices have evolved over the last century becoming more focussed on the known routes of transmission of infection, *i.e.* airborne, droplet and contact, and less based on rituals such as the use of disposable crockery and cutlery or the double bagging of waste from isolation rooms; additionally in the UK there has been a move away from dedicated isolation facilities (*i.e.* isolation wards) towards isolation in single rooms on general wards. [192 219]

Airborne spread can be defined as the spread of infections that are disseminated by airborne droplet nuclei or small particles in the respirable range, defined as $\leq$ 5μm in size and capable of being inhaled deep into the respiratory tract. These particles contain the infectious agent, which is capable of remaining infective over time and distance. Thus the susceptible individual need not be in close contact with the source patient. Examples include *Mycobacterium tuberculosis* and varicella-zoster virus. [220] The need for isolation in a single room, with, ideally, controlled ventilation to prevent the spread of these organisms is uncontroversial.

For infections that are spread by the droplet or contact route and for the latter only those organisms that are considered to be epidemiologically important *e.g.* bacteria resistant to multiple antibiotics and *Clostridium difficile*, placing the patient in a single room is considered to be an important

component of the necessary precautions to prevent transmission. [163 190 192 219-222] This is despite the fact that these organisms are spread primarily either by close face-to-face contact in the case of those organisms spread by the droplet route such as the influenza virus and *Neisseria meningitidis* or by direct and indirect contact.

1.4.1. Current guidance on isolation

There are currently no formal guidelines for patient isolation in England and Wales, *i.e.* endorsed by the Department of Health,. This contrasts with the USA where the CDC, a federal agency concerned with infection prevention and control, among other issues, has issued guidance on this subject. [192 220] The CDC guidance covers all aspects of isolation practice including: suitability of facilities; the nature of the required barrier precautions; and the USA regulatory framework, as well as listing the majority of organisms, diseases and scenarios for which isolation may be required with guidance as to the level of precautions to employ. The CDC guidance is based on the concept of 'transmission-based precautions' thus different levels of isolation are deemed appropriate depending on how the organism is transmitted *e.g.* airborne or contact transmission.

Although there is no UK equivalent of the above guidance a joint working group of the Association of Medical Microbiologists, British Infection Society, Hospital Infection Society, Infection Control Nurses Association and the Public Health Laboratory Service [now part of the Health Protection Agency]

have produced a review of hospital isolation and infection control related precautions. [219] This review supports in most respects the CDC recommendations, including the principle of transmission-based precautions but, unlike that guidance, does not attempt to provide an exhaustive list of organisms and the required level of precautions. Such guidance on isolation for specific organisms or conditions may be found in UK health department documents on, for example, tuberculosis, [223] viral haemorrhagic fever [224] and *Clostridium difficile*. [225]

1.4.2. Availability of single rooms and prioritisation of usage

When comparing USA and UK isolation practice it is important to be aware of the structural differences in their respective health-care facilities. Typically US hospitals are designed and built with rooms to accommodate one ('private') or two ('semi-private') patients. [226] Thus CDC guidelines are based on an almost certain availability of single (or at least usable-as single) rooms. UK hospitals in contrast are normally built with a variable number of single rooms per ward, a number that has historically been quite low. For example, and excluding a small number of specialist wards with all single rooms, the General Infirmary at Leeds has between none and six single rooms per (approximately) 25-30 bedded ward. Current guidance for the proportion of beds as single rooms in UK hospitals is limited to planning guidance applicable to new buildings and major refurbishments only, which takes as its starting point an assumption that a minimum of 50% of the beds will be single rooms; [227] [228] however, in reality very few NHS hospitals are

even close to this standard. NHS Estates in England (now defunct) in 2005 stated that "the NHS rarely provides more than 20% single rooms in its hospitals". [229]

The decision to base UK guidance for hospital design on a minimum 50% of single rooms is based on a number of factors in addition to the assumption that it will be valuable in the prevention of HCAI. In particular, single rooms provide privacy, dignity and confidentiality for patients and most, though not all, patients would choose a single room if available. In addition, single rooms are regarded as quieter and more conducive to being personalised in terms of levels of lighting, temperature and visiting times.

From the perspective of the healthcare organisation, single rooms provide greater flexibility in use, *e.g.* can be occupied by either gender and by all ages. Set against these potential advantages are issues of increased building costs and the possibility that NHS healthcare workers will have difficulty adjusting existing ways of working to suit a higher level of provision of single rooms. [230 231]

The disparity between the guidance on isolation of patients with epidemiologically-important organisms and the reality of single room provision makes all such guidance a 'counsel of perfection' [219] and necessitates that hospital personnel make choices regarding the

prioritisation of single rooms. These choices not only encompass infection-control requirements but necessarily also include other conflicting demands on the availability of single rooms, such as care of the terminally ill, patients who are disturbed and disruptive and patient choice.

There are few published reports of the requirements for, or the utilisation of single rooms for isolation of patients with epidemiologically-important organisms and/or infectious diseases. Two studies from Dundee, Scotland, have prospectively studied the usage of isolation rooms in a dedicated infectious diseases unit. [232] [233] In both studies they observed that this very limited and highly specialised resource was used inappropriately, with approximately half the patients (44.1% and 55.1%, respectively, in the two studies) admitted to the isolation rooms presenting no risk of infection transmission.

Two studies have undertaken repeated point-prevalence surveys of the use of single rooms on general wards, suitable for patient isolation. Barlow *et al.* [234] found that in three surveys an average of only 39.5% of such rooms (n = 129) were occupied by patients with a recognised risk of transmitting infection but that there were 28 of 79 (35%) patients, who were deemed to carry a risk of transmission, in open bays. Of these 28, seven were in an MRSA cohort leaving 21 in bays with patients not known to be colonised with epidemiologically important organisms such as MRSA and eleven of these

were considered to have at least one risk factor for increased transmission risk. The study by Doherty *et al.* [235] was limited to MRSA patients only but again found, on average, a large proportion (32%) not isolated or cohorted despite only 61% of suitable single rooms being in use for isolation.

The UK joint working party report suggests, as one possible way forward, the adoption of a formal risk-assessment tool for the assessment of need for isolation; the example they give is the 'Lewisham Isolation Priority System' (LIPS) [236]. 'LIPS' is a scoring system giving scores for a number of criteria including: route of transmission; significant resistance and the susceptibility of other patients and calculates from these scores a result that indicates the priority for isolation (Appendix B). Other similar risk-assessment tools have been developed and published. [237-239]

Although the authors of these tools have made anecdotal claims for their utility and effectiveness there is no evidence of them having been formally evaluated. Such a tested and evaluated tool would be potentially useful but it is unclear how such testing would take place as there is no 'gold standard' against which to measure the accuracy and the effectiveness of the tools. An initial approach might be to test the inter-observer reliability of the tools to identify if they are at least applied consistently.

1.4.3. Compliance with isolation precautions

Anecdotal evidence suggests that compliance with isolation precautions, in particular contact precautions, is sub-optimal. Afif *et al.*[240] observed compliance with isolation precautions for MRSA including the appropriate use of protective clothing and hand hygiene. Overall compliance from 488 observations was 28%. In a multivariate analysis the only significant predictor of poor compliance was the profession of the healthcare worker with occupational therapists and physiotherapists most compliant and housekeeping staff least.

A study by Cromer *et al.*[241] used an intensive feedback and education programme to achieve and sustain improved compliance with contact precautions to prevent transmission of antibiotic-resistant organisms. From a starting point of only 19% compliance their programme achieved a sustained mean daily compliance of 72%. They claim that this reduced the MRSA acquisition rate in their facility despite increased colonisation pressure; however they present no statistical analysis to justify the significance of this reduction.

Another intervention study, set in an ICU, utilised a targeted information flyer to increase compliance with isolations for MRSA; although this study reported a statistically significant increase in all the outcome measures for compliance ($p < 0.05$ for all; Fisher's exact test with Holm's correction for multiple testing), these were 'proxy' measures such as the availability of

appropriate equipment and the placing of signs on isolation room doors. It is unclear whether this demonstrates any measurement of actual compliance. [242]

Manian *et al.* [243] observed gown-wearing as part of contact precautions on both ICUs and general wards. From 1,552 observations they identified overall compliance of 73% (76% for healthcare workers). Weber *et al.* [244] observed compliance with all types of isolation protocols in three hospital-wide observational surveys. They found that compliance was mostly sub-optimal with compliance with contact precautions of 73%.

Another study that used 'proxy measures' for isolation compliance was unique in that it examined compliance with isolation precautions used as a matter of routine until the results of MRSA surveillance cultures were available (described as 'preventive barrier precautions'). [245] The authors found, even using these crude measures, compliance to be very low (range 3 to 62% for the various elements examined) and it is likely that actual compliance would be even lower.

1.4.4. Potential detrimental effects of isolation

A number of studies have been published that describe the potential adverse effects associated with placing patients in isolation. These include psychological morbidities such as extreme boredom, a risk of lowered or disturbed mood, a perception of stigmatisation; and depression. These

psychological morbidities have been identified previously in some isolated patients, although other authors have found little evidence of such detrimental effects. [246-250]

Other studies have identified other risks to patients in source isolation related to the risk of adverse events and reduced quality of care; Kirkland and Weinstein [251] observed that healthcare workers were only half as likely to enter the room of an ICU patient in isolation. This finding was reinforced by Evans *et al.* [252] who observed that isolated patients received fewer visits and were attended for less time by healthcare workers than patients who were not isolated, and partly reinforced by Saint *et al.* [253] who observed that attending physicians [consultants] were significantly less likely to visit medical patients in isolation (RR 0.49, 95% CI 0.3 to 0.79) but senior residents [specialist registrars] were not. Stelfox *et al.* [254] compared patients isolated because of MRSA with controls who were not isolated from both a general and disease-specific (congestive heart failure) population in a case-control study. They found that isolated patients were twice as likely to experience adverse events as patients who were not isolated ($p < 0.001$; Student's t test), were more likely to complain about the quality of their care ($p < 0.001$; Student's t test), and to have neither vital signs nor medical progress documented appropriately ($p < 0.001$ for both; Student's t test). In addition, there have been two case reports of isolation for MRSA being detrimental to proper and necessary rehabilitation. [255 256]

1.4.5. Isolation to control the transmission of multi-drug resistant organisms.

The evidence for the effectiveness of contact precautions, including placement in a single room, in preventing and controlling the transmission of multi-drug-resistant organisms (MDROs) has been systematically reviewed. [198] The authors of the review considered the literature published until June 2005 and, after excluding outbreak reports, identified 29 studies suitable for inclusion of which seven were deemed to be of high quality using a recognised assessment tool. They concluded that the findings of the studies were generally consistent and supported the use of contact precautions in reducing the transmission of MDROs but that they were methodologically weak and potentially subject to significant biases, including performance, selection, detection, attrition and investigator biases. In particular, virtually all of the published studies examined multiple interventions simultaneously thus making it impossible to measure the impact of individual components of a control programme. In addition, almost none of the studies measured the compliance with the intervention being tested. The authors recognise that their review is limited as they only reviewed English-language papers but they fail also to discuss or test for any potential publication bias and their search strategy makes no mention of 'grey' literature.

These findings are supported by recently-published guidance from the USA on the management of MDROs in healthcare settings. [222] The guidance

authors identified 104 published reports of interventions to control the transmission of MRSA, vancomycin-resistant enterococci (VRE) or multidrug-resistant Gram-negative bacilli. The median number of interventions per study was seven, though the authors comment that this may be an underestimate due to under reporting of initial interventions. Although there is an impressive consistency in the outcomes reported in their review, the authors do not describe any search strategy or assessment of methodological quality as part of their review process. It is likely that many, if not the overwhelming majority, of the studies they quote, given that they note that > 60% or them are reports of outbreaks, will suffer from the methodological weaknesses and systematic biases reported by Aboelela and colleagues. [198] The authors note that there are currently no studies that have directly compared standard precautions with standard plus contact precautions to control the transmission of MDROs but that a large multi-centre randomised trial is in progress comparing 'standard care' (standard precautions and collection but not reporting of screening cultures) with an enhanced strategy involving collecting and reporting screening cultures, routine glove use unless patients have had negative results from screening samples for MRSA and VRE and contact precautions for all identified cases of infection with MRSA and VRE. From the limited protocol information available for this trial, available on-line at: http://clinicaltrials.gov/ct/show/NCT00100386?order=1, it is not clear whether contact precautions will automatically include a single room or how

clinically-ascertained cases of MRSA and VRE infection will be managed under 'standard care'. In addition this trial is set in intensive care units and the results may not generalise to other populations.

1.4.5.1. Isolation to control the transmission of MRSA

Isolation in a single room or cohorting of affected patients is recommended for the control of MRSA in hospitals in the UK and other countries. [163 190 191] These recommendations are based on the potential for dispersal of staphylococci via airborne particles as well as through direct contact and on historical studies demonstrating control of staphylococcal transmission using isolation in a single room. [257-259] UK guidance also draws on the experience of other countries, in particular those of northern Europe, where aggressive control programmes appear to have been successful in preventing MRSA becoming endemic; [68 194 260 261] however, UK experience has matched that of many countries in that, despite initially adopting an aggressive control policy, MRSA has become endemic in most hospitals. This situation has occurred even where, initially, limited success in controlling MRSA has been demonstrated. [262]

Cooper *et al.* systematically reviewed the literature on isolation measures in the hospital management of MRSA; [197] their review identified 46 studies published up until the year 2000 that investigated the impact of isolation in a single room, isolation wards or nurse cohorting on the incidence of MRSA colonisation and/or infection. The authors were unable to conduct

meta-analysis of the available studies due to their heterogeneity and therefore presented their findings as a narrative summary of the quality and outcomes of each study. They concluded that the majority of the studies were methodologically weak due to poor design, major confounders and/or the risk of systematic biases and that virtually all combined isolation with at least one other simultaneous intervention, making it impossible to assess the relative contribution of isolation. They did note that six of the studies provided some evidence, consistent with a reduction in MRSA that was related to isolation, and with a relative lack of plausible alternative explanations. Of these six studies, only two provided any evidence that isolation in single rooms had a significant impact and of these two, one included multiple interventions including an 'extensive' hand hygiene programme and the other was set in a paediatric ICU, thus making it difficult to generalise the results. From this comprehensive review of the evidence, Cooper and colleagues concluded that there was little evidence to prove that current strategies for managing MRSA, including isolation, are ineffective, but that the evidence to demonstrate that such strategies are effective is limited.

These conclusions are supported by a second systematic review of the efficacy of patient isolation for the control of MRSA in hospitals, [263] this review also included studies published until 2000 but, unlike the former review, was limited to studies published after 1980. The authors of this

review concurred with Cooper and colleagues, describing the quality of the available evidence as having "significant methodological weaknesses"; and concluded that there was a lack of proven clinical benefit for isolation, though they also cautioned against discontinuing current practice without further research.

A third systematic review, published in 2006, noted the findings of the reviews described above and identified studies published after the period already covered and up until June 2004.[168] This review identified four further observational studies that were considered to be of an acceptable quality, all of which supported the view that isolation contributed to reductions in MRSA prevalence; however one was set in a dedicated cohort ward rather than using single rooms for isolation [264] and two reported multiple interventions [265] [266] making it impossible to identify the relative contribution of isolation precautions alone. The fourth study [267] compared the results of a questionnaire about infection-control processes in German intensive care units with infection rates reported to that country's national surveillance system; multivariate analysis of the results demonstrated lower rates of MRSA infection associated with the routine isolation of MRSA patients (OR 0.36, 95% CI 0.17 to 0.79); again, however, these results may not be easily extrapolated to populations who are not nursed on ICU facilities, where patient risk factors and staff-patient ratios are very different. There have been further studies published since the time covered by these three

systematic reviews; using the criteria for study selection employed by Cooper *et al.* [197] (see Appendix C) eleven articles were identified: Pastila *et al.* [268] describe the control of a multi-hospital, ten-year outbreak of epidemic MRSA using a combination of screening and isolation/cohorting as well as an education programme. They successfully controlled the outbreak, returning MRSA incidence to a low annual baseline of under five cases per year. The data were analysed retrospectively and there are no data points given either before or after the epidemic period thus making if difficult to exclude the contribution of regression to the mean effects to the outcome presented. Tomic *et al.* [269] prospectively measured both MRSA incidence and the proportion of MRSA cases deemed to be acquired in their institution, both before and after the institution of multiple interventions designed to detect cases and to prevent nosocomial transmission. They found no significant change in MRSA incidence over five years but did identity a significant increase in the proportion of all MRSA cases that were deemed as imported ($p < 0.001$; χ^2 test for trend). It is plausible that their interventions prevented a significant overall rise in MRSA incidence but the relative impact of isolation cannot be identified due to the number of simultaneous interventions. A study by Cepeda and colleagues, [270] in two intensive care units, prospectively studied the impact of isolation in a single room as a single intervention, on MRSA acquisition rates and found that there was no change, either before or after adjustment for a number of potential confounders, in MRSA acquisition whether patients harbouring

MRSA were moved to single rooms or not. This prospective study of a single intervention provides strong support for the theory that isolation in a single room does not, in the ICU setting, reduce MRSA transmission. Observed hand hygiene compliance was very low (21% of hand hygiene opportunities taken) and this may partly explain these findings; nevertheless this only reflects 'real-life' clinical practice.

Schelenz *et al.* [203] in a retrospective analysis, reported a significant decrease in nosocomial MRSA acquisition and MRSA bloodstream infections ($p = 0.003$ and 0.014, respectively; χ^2) in a cardiothoracic ward, following interventions targeted at MRSA infection. However they implemented twelve different interventions simultaneously, making assessment of the relative contribution of isolation impossible.

A report by Khoury and colleagues [271] describes the successful and prolonged elimination of MRSA from a neonatal intensive care unit following an outbreak. The fact that no cases occurred in the two and a half years following the intervention suggests that the intervention was effective, notwithstanding any regression to the mean effect; however the setting is highly specific and thus the findings are not easily generalised and again, multiple interventions were introduced at the same time.

Huang *et al.* [272] retrospectively analysed the sequential implementation of four different infection control interventions in intensive care units, unusually these were implemented one at a time. Of the four interventions; maximal sterile barrier precautions for central venous catheter insertion, introduction of alcohol-based hand rub, a hand hygiene campaign and routine surveillance swabs for MRSA with contact precautions for all identified cases, only the latter had an impact on rising incidence of MRSA. Interestingly, this impact was found both within the ICUs themselves and in the wider hospital population. As the apparently effective intervention was the last to be applied it could be argued that the impact was a cumulative one, but the effect was sustained for more than one year.

A report by Safdar *et al.* [273] describes an MRSA outbreak in a burns unit and ascribes termination of the outbreak to the use of pre-emptive (*i.e.* for every patient, regardless of MRSA status) barrier precautions; however the authors present the MRSA incidence data in three phases; pre-, during and post-intervention and the MRSA incidence rates pre and post intervention are not significantly different (the 95% CI overlap) strongly suggesting regression to the mean as a plausible alternative explanation for their findings.

Shitrit *et al.* [200] investigated the impact of introducing surveillance for MRSA carriage in high-risk patients (those deemed most likely to be carriers) and

contact precautions for all those found to be positive on hospital-wide MRSA bacteraemia incidence over a two and half year period (13 months before and 14 months after). They found a significant reduction in bacteraemia cases ($p < 0.001$; Student's t test); however they note that during the pre-intervention period MRSA bacteraemia cases had increased, including several 'outbreaks'. The authors do not provide data for the pre-increase baseline period, it is therefore impossible to exclude regression to the mean effects. In addition it is unfortunate that data for nosocomial MRSA acquisition are not given as this may better reflect the impact of isolation/contact precautions, which are designed to prevent transmission rather than bacteraemia. Of course bacteraemia may be an appropriate marker for the overall burden of MRSA, but this is unproven.

The systematic review by Cooper *et al.* [197] made recommendations as to the conduct and reporting of 'interrupted time series' intervention studies. The report by Curran *et al.* [274] follows these conventions in reporting the use of a temporary cohort ward to reduce the incidence of MRSA in vascular surgery. They report a sustained reduction in MRSA incidence through the cohorting of patients and nurses; interestingly this reduction has been sustained despite the closure of the temporary facility, which the authors ascribe to the ability to identify and isolate all cases in the available single rooms following the reduction in MRSA prevalence. The authors note that they used additional interventions simultaneously such as enhanced cleaning and

support for early discharge and that these could have contributed to the outcome being measured. In addition, the fact that the reduced incidence has been sustained despite the closure of the cohort may suggest that factors other than the cohort *per se* may have had an impact. Nevertheless this is a well-conducted and reported study that supports the use of separation of patients harbouring MRSA from those who do not carry this bacterium.

Harbath *et al.* [275] describe the use of rapid screening, utilising multiplex polymerase chain reaction (PCR) testing and pre-emptive isolation for those deemed to be at high risk of MRSA colonisation on admission to ICUs at a large tertiary referral centre. Their results are not consistent, as they found a reduction in nosocomial MRSA acquisition in the medical but not the surgical ICU at their facility (RR 0.3, 95% CI 0.1 to 0.7 and RR 1, 95% CI 0.6 to 1.7, respectively). The authors suggest this may be due to differences in the two populations. If the effect is due to the intervention, and if the observation is true, this suggests that the effect is highly specific and cannot be extrapolated beyond the population studied.

An observational study by Bracco *et al.* [276] reported the incidence of acquired MRSA (and other nosocomial pathogens), comparing occupants of open bays with those of single rooms. Using multivariate analysis they found that occupants of single rooms were significantly less likely to acquire MRSA

(OR 0.65, 95% CI 0.42 to 0.98). There were, however, significant differences between those patients in single rooms and those in bays, including receipt of antibiotics, and there is inadequate description of the multivariate analysis in the report to determine if these differences were controlled for in the analysis. Gould *et al.* [204] conducted a prospective interventional study with historical control data in an ICU, into the impact on MRSA incidence of introducing screening for MRSA with isolation and continuous topical decolonisation treatment of identified carriers throughout their ICU stay. While their results show a convincing and sustained reduction in MRSA incidence (using time-series regression analysis $p = 0.005$), it is not possible to identify the specific effect, if any, of the isolation/contact precautions *vs.* the extensive use of topical decolonisation treatments.

In summary, these eleven more recently published studies, while in some cases demonstrating improvements in design, analysis and reporting of longitudinal and 'before and after' interrupted time series intervention studies, demonstrate that, though highly plausible the case for isolation or cohorting of patients to reduce the incidence of MRSA is not proven. Many of the studies fail to consider potential biases or other plausible explanations for the effects found or report multiple simultaneous interventions thus making it impossible to identify the relative effect of an individual intervention such as isolation. Others, for reasons of clinical priority and logistics, are set in untypical populations *e.g.* adult or neonatal ICU patients and even when

their results support the use of isolation such results cannot be necessarily generalised to the wider hospital population.

In addition to reviewing the literature systematically, Cooper and colleagues used both stochastic and deterministic mathematical models to study the effects of opening an isolation ward on MRSA transmission and prevalence in the epidemic and endemic settings.[197] As previously discussed, all modelling is limited by the necessary assumptions that are made; in this case the authors assumed both that the population would be homogenous with regards to risk of MRSA acquisition, and that no transmission occurred outside of the hospital. Both of these assumptions are likely to be flawed, the first especially so. From their modelling the authors concluded that such an intervention could, over time, reduce MRSA transmission and prevalence but that this may be dependent on several factors, in particular; the timing of the intervention (the earlier in the epidemic the more likely to succeed), the level of the resource provision *i.e.* the size and potential for scaling-up of the isolation ward, and some element of chance or stochastic variation.

2. Aims of the current study

2.1 Introduction

The recommendation to isolate patients with communicable diseases or organisms of epidemiological importance has been described as a counsel of perfection. There is a general perception that although isolation may be recommended, in many cases it is not achieved due to a lack of facilities and conflicting priorities for the use of those facilities. Currently, in the UK, there is no-evidence based guidance on the required number of single rooms per ward for the purpose of isolation or other patient management needs (*e.g.* terminal care).

There is a lack of published data on the extent of the problem of failing to isolate patients appropriately, on the reasons for such failures or on the impact of these failures on the control of communicable diseases and epidemiologically important organisms. In particular there are few studies that directly examine the relationship between 'failure to isolate' and the prevalence of MRSA.

2.2 Aims

2.2.1 Prospective evaluation of the incidence of isolation failure

- To identify why ward staff are unable or unwilling to isolate patients, following risk assessment and advice from an infection control nurse.

- To identify further the duration of such "failures to isolate" and the ongoing placement of the affected patients until such time as isolation is deemed no longer necessary or the patient is discharged from hospital or dies.

- To determine the extent of isolation facilities and how closely this provision meets current infection control needs, particularly in respect of MRSA.

- To establish if there is any correlation between rates of 'failure to isolate' and the incidence, by ward, of MRSA from samples submitted for clinical purposes.

2.2.2 Prospective observational cohort study of MRSA acquisition comparing index cases who were isolated with those who were not isolated

- To determine the adjusted relative risk of secondary cases of MRSA following successful and unsuccessful attempts to isolate patients with MRSA.

- To identify independent risk factors for MRSA acquisition

3. Materials and Methods

3.1. Ethics

The studies were approved by the Leeds Research Ethics Committee and registered for research governance purposes with the research and development department of the Leeds Teaching Hospitals NHS Trust.

3.2. Study setting

The study was undertaken in the Leeds General Infirmary (LGI), which is one of two large hospitals that form part of the Leeds Teaching Hospitals NHS Trust. The hospital has approximately 1150 beds distributed across 60 wards, and is typical of a large UK NHS teaching hospital, with a wide range of medical and surgical specialities (for both adults and children) and a number of regional specialities, including neonatal services, cardiothoracic surgery and neurosciences. The hospital has 45 ITU beds and a renal unit, but does not have an on-site isolation/infectious diseases unit. There is a wide range of building types built between the 19th and late 20th centuries. MRSA prevalence at the LGI, as measured by the number of MRSA bacteraemia cases per 1000 patient days, is similar to other large teaching hospitals and comparable with or higher than other UK hospitals in general [277], thus MRSA may be described as endemic within the LGI.

During the study there were no changes to the policies and protocols in place for the isolation of patients with potentially transmissible infections or

for the management of MRSA. In addition there were no major alterations to the Trust antimicrobial policy.

3.2.1 Policies for the infection control management of MRSA and for isolation of patients colonised or infected with epidemiologically-important microorganisms or with communicable diseases.

Screening for MRSA was limited to patients admitted from countries outside of the UK and only after discussion on a case-by-case basis with a microbiologist. Topical decolonisation agents including mupirocin nasal cream and triclosan body washes were only used in certain high-risk specialities *e.g.* critical care units and what were deemed to be high-risk surgical specialities; in addition, patients undergoing major operations in certain specialities received a prophylaxis regimen to prevent infection with *S. aureus* comprising nasal mupirocin and triclosan washes, without pre-operative screening for MRSA.[210] In any situation where they were used, topical decolonisation agents were only used for a single course per patient.

Isolation in single rooms or grouping together in bays, known as 'cohorting', of patients identified to be colonised or infected with MRSA was done on the basis of a risk assessment. The risk assessment took into account both the potential for dissemination of MRSA from the identified patient and the vulnerability of the other patients on the ward or department to the consequences of MRSA colonisation and the potential of subsequent infection.

The potential for dissemination of MRSA from the identified patient was considered to be greater if MRSA was identified from sputum or from an leaking wound or one that required frequent changes of dressing and also if the MRSA was considered to be causing active infection rather than colonisation. Increased dissemination was also considered likely if the patient had an exfoliating skin disorder such as eczema or psoriasis. Groups of patients considered to be more vulnerable to the consequences of MRSA colonisation or infection included those at increased risk of infection in general, *e.g.* the critically ill or immune-suppressed as well as those undergoing most types of surgery. For the full policy for the infection control management of MRSA in place during the study period refer to appendix E

For all situations in which a patient was known or suspected to be colonised or infected with an epidemiologically-important microorganism or to have a communicable diseases, the decision to isolate or not to isolate a patient in a single room or to place the patient in a cohort with other patients affected by the same organism or condition was made after a risk assessment made collaboratively between the clinical staff caring for the patient and the infection control team. The risk assessment was not detailed in any written policy, as the 'source isolation policy' (appendix F) was primarily intended to describe the necessary precautions once the decision to isolate or place in a cohort had been made. Such risk assessments gave priority to infections

transmitted via the airborne or droplet route (see 1.4) and when considering those infections spread primarily by contact, priority for isolation took into account the factors described in the Lewisham Isolation Priority System (appendix B) *e.g.* any significant resistance to antimicrobials, the susceptibility of other patients nearby, the prevalence of the organism and the potential for its dispersal. The Lewisham system was not, however, adopted formally within the organisation.

3.3 Prospective evaluation of patient isolation requirements and isolation room capacity.

3.3.1. Study design

The study was a prospective, observational study without any intervention.

3.3.2. Data collection

Data were collected on every requirement for patient isolation for infection-control reasons during the period April 2003 to March 2004. Following risk assessment in collaboration with clinical staff caring for the patient, each requirement for isolation was made by an infection-control nurse (or doctor). The outcome of the risk assessment and, in cases where this indicated the need for isolation, whether this was achieved, was recorded ('isolation not required', 'required and achieved', or 'required but not achieved'), with details of the factors influencing the assessment, on a database (Alert, ISoft plc, Manchester, UK).

Successful isolation included both isolation in a single room and the placement of the patient in a cohort of patients with the same pathogen or disease. When the outcome was 'isolation required but not achieved' (henceforth referred to as 'failure to isolate') a single investigator followed up the case and ascertained the following: the reason(s), as expressed by the ward nursing staff, why the requirement for isolation was not possible; the location of the patient; and the duration of the 'failure to isolate' (to the nearest whole day).

To calculate the total number of patient days of exposure, to cases of 'failure to isolate', 100% bed occupancy was assumed. The total number of patient days of exposure to cases of 'failure to isolate' is calculated as:

(number of beds in bay –1) x (duration of 'failure to isolate' in days).

Using 100% bed occupancy is necessarily crude as the true bed occupancy per day on each ward and each multi-bedded room was unknown. To allow for this, the outcome was recalculated using low and high estimates of bed occupancy, based on local knowledge and experience, of 85 and 95%.

Four point-prevalence surveys were performed of occupation of single rooms at three-month intervals to ascertain the reasons for and distribution of usage of single rooms for isolation. The number and proportion of total beds that were in single rooms were recorded by ward.

3.4. Prospective comparison of 'failure to isolate' patients with clinically ascertained MRSA and number of new clinical MRSA isolates by ward.

3.4.1 Study design

The study was a prospective observational study without any intervention, combined with prospective surveillance of the incidence of MRSA identified from specimens obtained for clinical reasons over the same period.

3.4.2. Data collection

The incidence of new MRSA isolates obtained by diagnostic testing (as opposed to by screening) per ward was measured. A new MRSA isolate was defined as MRSA identified in a clinical specimen taken $\geq$ 72 hours after the patient's admission when there was no known history of MRSA colonisation or infection. MRSA isolated < 72 hours after admission was designated as 'community-acquired'. If the patient had been transferred from another ward in the same hospital within the previous 72 hours, the MRSA was assigned to the previous ward. The rate of 'failure to isolate' of patients in whom MRSA was identified from specimens obtained for clinical reasons and for whom a member of the infection control team had required isolation, per 100 isolation requirements was calculated for each ward thus:

$$\frac{\text{Number of 'failures to isolate' during study period}}{\text{Number of requests for isolation during study period}} \times 100$$

3.5. Prospective observational study of MRSA acquisition comparing the contacts of index cases who were isolated with those who were not isolated.

3.5.1. Study design

The study was a prospective, observational study without any intervention.

3.5.2. Power calculation

Any *a priori* power calculation could only guide the feasibility of the study as the period for data collection was limited to one calendar year for resource and logistical reasons. There were no pilot or published data on which to base a power calculation, however a crude calculation, using the methodology described by Altman [278] and assuming zero transmission from isolated index cases, indicated that 314 contacts would need to be included to detect a difference in MRSA transmission of 5% (at 85% power) and 191 contacts to detect a 10% difference (*i.e.* 0% of contacts of isolated index cases and $\geq$ 10% of contacts of non isolated cases acquiring MRSA).

Less than 5% difference was deemed to be too low to be clinically acceptable as a rationale for isolation but it was estimated, based on local historical data, that approximately 300 contacts would be available within the 12-month period of data collection. Thus the study was deemed to be feasible in the timescale available.

3.5.3. Data collection

Data were collected prospectively for one calendar year from August 2004 to July 2005. An index case was defined as a patient from whom MRSA has been identified in a specimen obtained for clinical purposes and from whom MRSA has not been identified during their current hospital stay.

Following identification of an index case and a recommendation to isolate there are two possible scenarios: 'the patient isolated' or 'the patient not isolated and remains in a multi-bedded bay or room'. In each situation the decision to recommend isolation was taken by either an Infection Control Nurse or Consultant Medical Microbiologist. This assessment took into consideration those factors that may increase or decrease the risk of transmission to, and subsequent clinical infection in susceptible patients using the guidance that was extant at the time of the study. [189] In each scenario, patients adjacent to the index case (*i.e.* in the same bay or in adjoining and facing beds, depending on ward layout) were identified. These adjacent patients had up to three serial nasal swabs, taken at the intervals described below, to determine whether MRSA acquisition occurred. Swabs were taken using a single sterile swab to sample both anterior nares of each patient. Serial swabbing started within 24 hours of the identification and risk assessment with isolation, or not, of the index case (described hereafter as day 0). Subsequent swabs were taken at; swab 2 - between 48 and 72 hours after day 0 and swab 3 - on the day of discharge or transfer or day 14

whichever occurred first. All swabs were processed within two hours of collection.

The use of nasal swabs without enrichment was a pragmatic choice, based on anecdotal experience of point-prevalence surveys. There is a lack of high-quality evidence on the optimal strategy for identification of MRSA colonisation; [163] nasal screening alone, however, can identify > 90% of colonised individuals [279] and is considerably less intrusive than swabbing multiple sites which may have caused patients to refuse their consent. In addition, there was no requirement to pool swabs from different body sites in this study which eliminated one advantage of using an enrichment broth. There was also some concern that enrichment may identify very small numbers of MRSA in an individual that do not represent genuine colonisation but, rather, transient carriage only.

Contacts in whom MRSA was identified by the screening specific to this study did not become index cases in their own right unless MRSA was subsequently isolated from a clinical specimen. In practice this occurred only rarely and the subsequent contacts of these 'contact becoming index' cases were different individuals from those of the original index.

3.5.3.1. Risk factor data

Data were collected on risk factors in both index cases (risk factors for increased transmission) and contacts (risk factors for acquisition). Individuals with clinical infection, particularly of the respiratory tract or large wounds *e.g.* burns and those with exfoliating skin disease are considered to be more likely to be 'dispersers' of staphylococci including MRSA thus making transmission more likely. [189] For each index case, in addition to basic demographic data and location, data were collected on: the type of specimen from which MRSA isolated, the presence or absence of symptoms of infection and the outcome of the infection-control risk assessment (isolation required or not).

For contacts, in addition to basic demographic data and location, data were collected on putative risk factors for MRSA acquisition (see 1.3.5.1) *i.e.* presence of intravascular catheters, pressure sores, surgical procedures, underlying disease severity (Charlson co-morbidity index [280-282] and see Appendix D), length of hospital stay (prior to day 0), nasogastric tube, enteral feeding, number of ward transfers (prior to day 0), dermatological condition and exposure to antibiotics within the last month.

3.5.1. Microbiological methods

3.5.1.1. Identification of MRSA

Nasal swabs were streaked onto Columbia blood agar (E&O Laboratories Ltd, Bonnybridge, UK) and incubated aerobically at 37° C for 48 hours. Colonies resembling *Staphylococcus aureus* were tested using latex agglutination for bound coagulase, protein A and capsular polysaccharides (Pastorex Staph-Plus, Bio-Rad, Marnes-la-Coquette, France.) Positive latex agglutination tests were confirmed as *S. aureus* by spot inoculation onto deoxyribonuclease test agar (E&O Laboratories Ltd.), incubation overnight (minimum 15 hours) at 37° C and flooding with 1M hydrochloric acid with visual inspection for deoxyribonuclease activity. Susceptibility testing to meticillin was performed by incubation overnight at 30° C on Iso-Sensitest agar (E&O Laboratories Ltd) overlaid with meticillin 25 µg strips (Mast Diagnostics, Merseyside, UK) Positive (MRSA NCTC 10442) and negative (meticillin sensitive *S. aureus* NCTC 6571) controls were included with each test.

Local data and experience support the utility and accuracy of using meticillin strips to determine susceptibility to meticillin in *S. aureus* in epidemiological studies as opposed to the testing of clinical specimens (Mark H Wilcox; personal communication). The definitive test to identify resistance to meticillin is to determine the presence of the *mec* gene using molecular techniques however this was considered to be impractical and too costly for the purpose of this study.

3.5.4.2. 'Phage typing

Study isolates of MRSA and 12 control strains were inoculated into peptone water and incubated overnight at 37° C. Seven of the control strains used were MRSA including EMRSA 15 and EMRSA 16 After heat-shocking at 56° C for 2 minutes [283] [284] inoculated peptone waters were poured onto phage agar plates (Leeds Teaching Hospitals, Department of Microbiology), excess liquid removed and allowed to dry. After drying, plates were inoculated with the phage pattern shown in figure 1 at 100 x Routine Test Dilution (RTD) using a multipoint inoculator and incubated overnight at 30° C. Plates were read visually and checked by a second observer who was blinded to the results recorded by the first observer. Disagreements in interpretation were resolved by referral to a third colleague to achieve consensus.

The results were recorded by looking for visible plaques in the confluent stapyloccocal growth and recorded as follows:

0 plaques = no reaction

1 to 9 plaques = weak reaction (with the number of plaques recorded)

10 to 19 plaques = weak reaction

20 to 50 plaques = strong reaction (noted as '+')

> 50 plaques = strong reaction (noted as '++')

Any tests considered to be inconclusive or with no reactions were repeated.

Figure 1. Block loading pattern of bacteriophage at 100 x Routine Test Dilution (100x RTD) for 'phage typing of MRSA using a multipoint innoculator

932 83C

29	52	52A	79	80
3A	3C	55	75x*	95
6	42E	47	53	54
75	77	83A	84	85
81	94	96	88A	90

* bacteriophage 75 at 1000 RTD

3.5.5. Pulsed Field Gel Electrophoresis (PFGE)

3.5.5.1. Descriptions of buffer solutions used in PFGE

TEN buffer (200 ml solution) – 20 ml of 1 Molar(M) TRIS-HCl solution (pH 8.0), 40 ml 0.5 M EDTA Na_2 and 1.76 g sodium chloride in 140 ml distilled water.

EC lysis buffer (400 ml solution) – 2.4 ml of 1 M TRIS-HCl solution (pH 8.0), 23.36 g sodium chloride, 80 ml 0.5 M EDTA Na_2, 2 g N-lauryl sacosine and 0.8 g deoxycholic acid in 318 ml distilled water.

TE buffer (500 ml solution) – 5 ml of 1 M TRIS-HCl solution (pH 8.0) and 1 ml 0.5 M EDTA Na_2 in 494 ml distilled water.

3.5.5.2. PFGE method

All MRSA isolates that were indistinguishable by 'phage typing were characterised further using PFGE. Isolates were incubated in 5 ml 2x yeast extract/tryptone broth + 0.5% glycine broth at 37° C overnight on a rotary shaker set at 100 revolutions per minute (rpm) . After harvesting from 0.7 ml broth using low speed (6,500 rpm) microcentrifuge and washing with TEN buffer, cells were harvested as before and lysed using 2 µL of 1 mg/ml lysostaphin with 0.3 ml EC lysis buffer. After vortexing, the bacterial suspension was mixed with 0.3 ml molten 2% low melting point agarose. After vortexing briefly, 100 µL of the above solution was pipetted into block moulds and cooled at 4°C for 20 minutes. Once cooled, agarose blocks containing bacterial DNA were incubated for 1 hour at 37° C in EC lysis buffer and 1 hour at 55° C in TE buffer.

After four washes in TE buffer for 30 minutes, blocks were stored at 4° C prior to digestion and electrophoresis. Digestion of the bacterial DNA within the blocks was achieved by incubating approximately 1/3 of each block in 10 units of *Sma*I restriction endonuclease for 4 hours at 30° C. The PFGE gel was assembled by transferring one digested block onto each tooth of the gel comb and the pouring of 100 ml of molten 1% PFGE-grade agarose gel. A λ DNA ladder (BioLabs, New England) was also loaded onto each end of the gel as a size reference for the digested fragments. The λ ladder contained successively larger concatemers of λ DNA at 48.5 kilobase intervals from 48.5 to 727.5 kilobases. Following this, the gel was allowed to

set before PFGE was performed using the CHEF II MAPPER Pulsed-Field Gel Electrophoresis System (Bio-Rad Laboratories, Hemel Hempstead) with settings of: field strength 6 volts/cm, pulse times: 5 - 15 seconds for 10 hours followed by 15 - 60 seconds for 13 hours (total running time 23 hours). Following electrophoresis, gels were stained with 0.1 µg/ml ethidium bromide for 1 hour on a rotating platform and were then rinsed in distilled water. Gel images were recorded using Gene Genius Gel Imaging System (Syngene Ltd.).

DNA profiles for index cases and contacts were analysed using BioNumerics software (Applied Maths Biosystemetica) Dendrograms were constructed and comparisons made using the unweighted pair group method using the Dice correlation coefficient.

The relatedness of the index case and contact strains was assessed using the criteria for bacterial strain typing formulated by Tenover *et al* [66] and considered suitable for short term epidemiological studies. For the purposes of this study where indexes and contacts were epidemiologically connected to each other in time and place isolates were considered to be related if they met the criteria for 'indistinguishable' or 'closely related' but not if they were 'possibly related' or 'different' as described by Tenover and colleagues (Table I)

Table I: Relatedness criteria for bacterial strain typing (adapted from Tenover *et al* [66])

Relatedness	Number of independent genetic differences	Number of band differences
Indistinguishable	0	0
Closely related	1	2-3
Possibly related	2	4-6
Unrelated	3 or more	7 or more

3.6 Statistical analysis

Continuous non-parametric data were compared using Spearman's ρ correlation coefficient. Analysis of categorical data was done using Pearson's χ^2 or Fisher's exact test as appropriate. The mean values of non-parametric data were compared using the Wilcoxon Rank-Sum Test. Analysis of risk factors using both categorical and continuous predictor variables with a categorical dependent variable was performed using forced entry multivariate logistic regression analysis. All risk factors that were significant at the $p < 0.2$ level were included in the model. The model fit and explanatory value were assessed using the Nagelkerke R^2 statistic and its associated χ^2 statistic as well as examination of the standardised residuals, Cook's statistic for standardised leverage and Dbeta statistics for all predictor variables. [285] In all cases $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS Version 11.5.0 (SPSS Inc. Chicago, USA).

4. Results

4.1. Prospective evaluation of patient isolation requirements and isolation room capacity

During the 12-month data-collection period there were 845 requirements for patient isolation for the purposes of infection control, of which 185 (22%) were considered as 'failures to isolate' within the first 24 hours from the time of risk assessment. Figures 2 and 3, respectively show the proportions of requests per pathogen/infection category, and the 'failures to isolate' as proportions of the total requests per pathogen/infection category. The reasons for 'failure to isolate' are detailed in Table II.

Table III details the breakdown of provision of single room, the demand for isolation facilities (expressed as number of requirements for isolation per 1000 patient days) and the number of 'failures to isolate' per 100 requests by clinical speciality.

A comparison between the proportion of beds that were single rooms and the number of 'failures to isolate' per 100 requirements (by ward) is shown in Figure 4; there was a statistically-significant inverse correlation between these two variables (Spearman's ρ = - 0.372; p = 0.002).

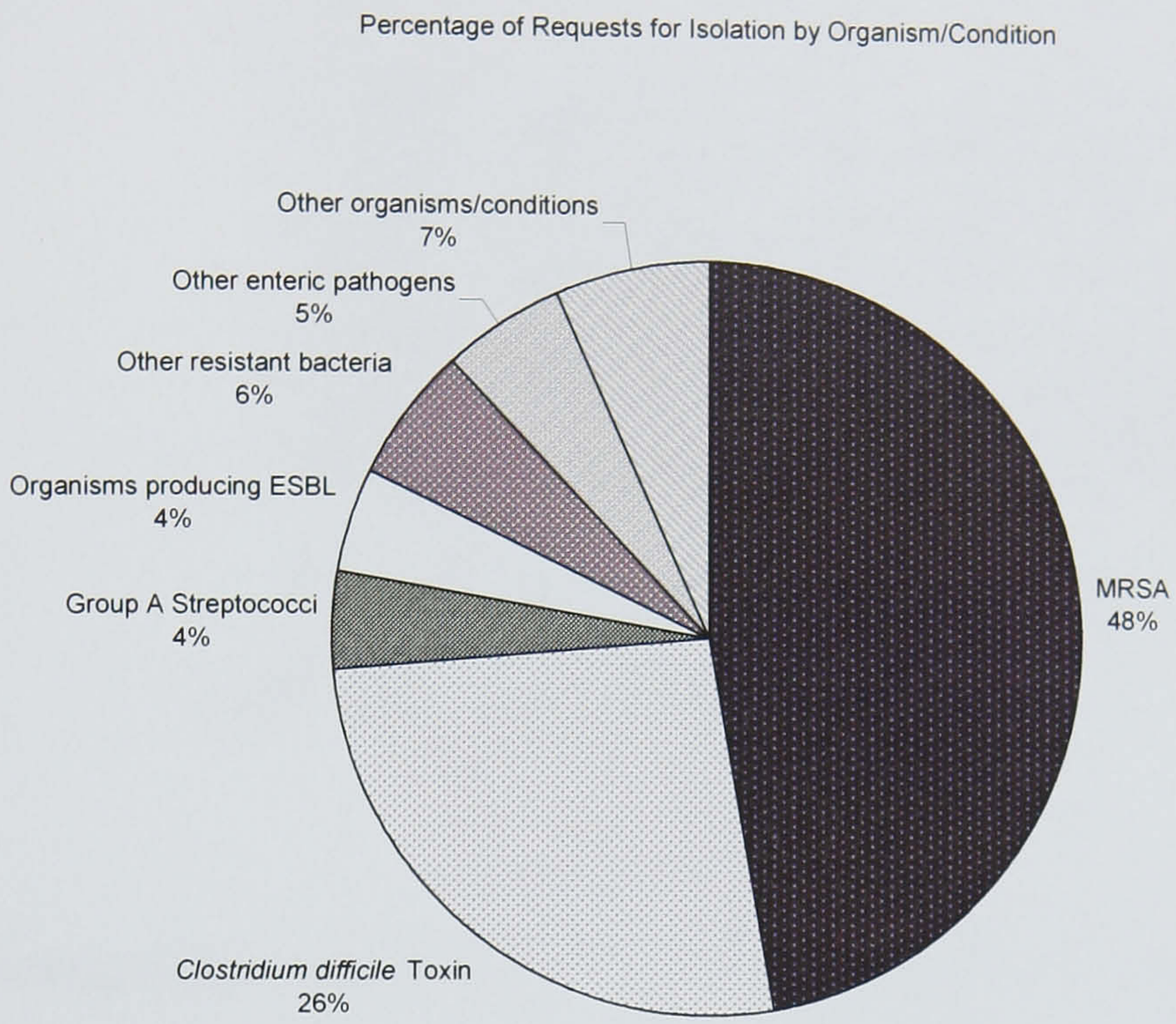
Over the four point-prevalence surveys the total numbers of available hospital beds varied between 1129 and 1151, and the numbers of single rooms between 194 and 207 (17-18% of all hospital beds). The median

number of single rooms (percentage of total beds) by hospital wing in order of the age of the buildings (oldest first) was 2 (16%), 3 (17%) and 2 (18%). There were 25 to 36 unoccupied single rooms (13-17% of all single rooms) and 24 to 36 (12-19%) were being used for isolation of patients for the purposes of infection control. Between 4 and 6 patients were in single rooms for 'protective isolation', the majority on the haematology ward.

The median duration of 'failure to isolate' was four days (inter-quartile range two to eight days, range 1 to 31 days). In one year, assuming 100% bed occupancy, there were ~3,500 patient days of exposure to cases with potentially transmissible pathogens when isolation was not possible. As 100% bed occupancy is not the norm in a typical acute hospital but bed occupancy rates are generally high, the above estimate can be recalculated using a realistic range of bed occupancy estimates, based on local knowledge and experience, of between 85% and 95%.

A bed occupancy estimate of 85% would give an estimate of ~3000 patient days of exposure and using 95% gives an estimate of ~ 3,300 patient days.

Figure 2 Distribution of reasons for isolation for the purposes of infection control by organism or condition

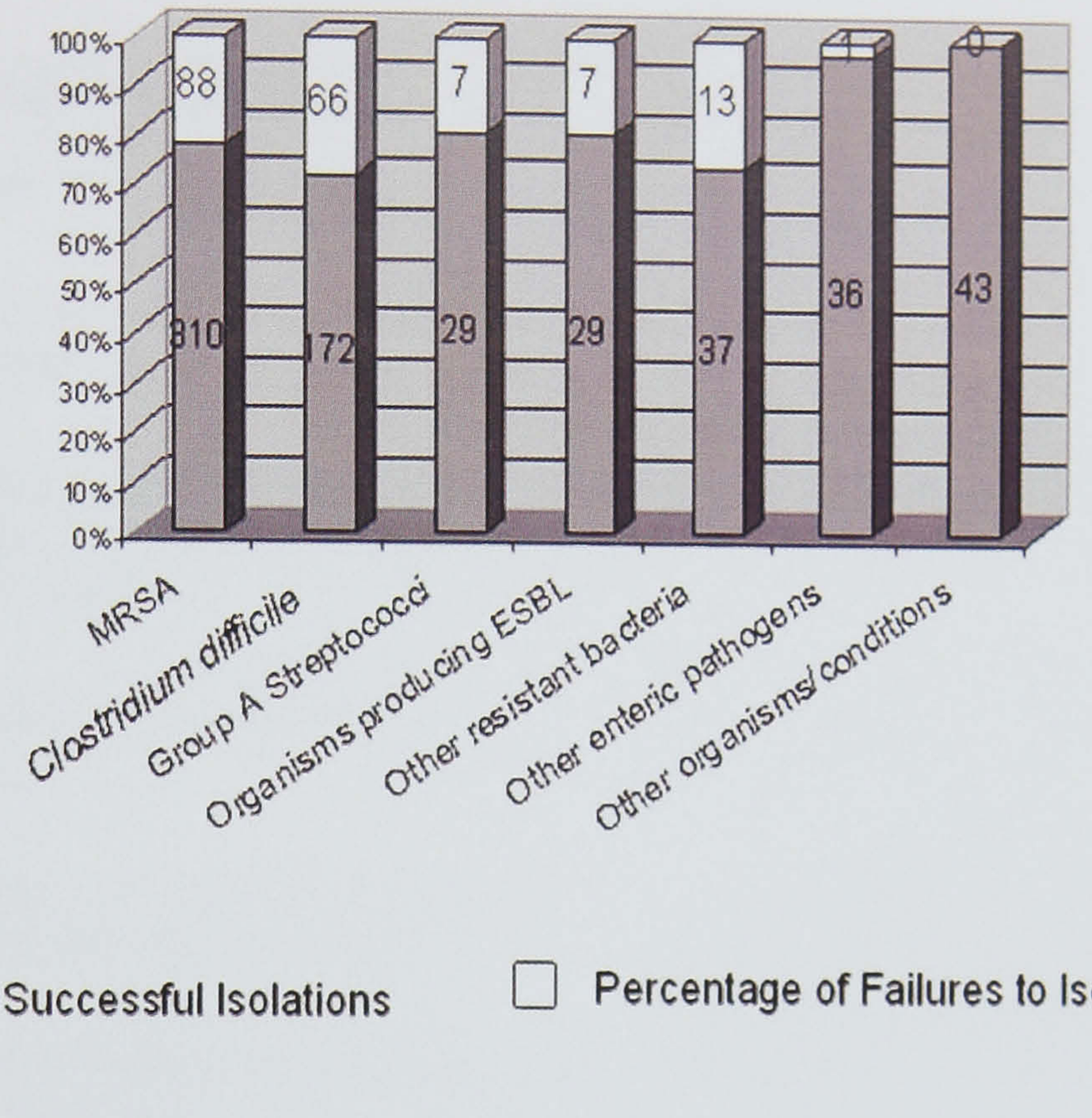


"Other resistant bacteria" – includes glycopeptide-resistant enterococci, penicillin-resistant pneumococci, multi-resistant Gram-negative bacteria (other than those that produce an ESBL) and *Acinetobacter* spp.

"Other enteric pathogens" – includes all enteric pathogens except *Clostridium difficile* (including suspected infectious diarrhoea and vomiting).

"Other organisms/conditions" – includes pulmonary tuberculosis (known and suspected), chicken pox and shingles, respiratory viruses and meningococcal infection.

Figure 3 'Failures to isolate' as a proportion (numbers of cases given in the bars) of the total requirements per organisms or condition



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"Other organisms/conditions" – includes pulmonary tuberculosis (known and suspected), chicken pox and shingles, respiratory viruses and meningococcal infection.

Table II Categories of reasons given by ward staff for 'failures to isolate' patients (n = 185*)

Reason for 'failure to isolate'	No. of occurrences*
Ward/dept. has no single rooms	53
Single rooms occupied with isolated patients (infection control reasons)	63
Male/female bed availability (*e.g.* all males in single rooms and no male empty beds on ward)	26
Patient reasons (safety, observation, behavioural *etc.*)	28
Rooms occupied – other reasons (*e.g.* terminal care or disruptive patient)	29
Others (*e.g.* room being refurbished, ICU full & too busy to manage transfer, staffing)	9

* Each 'failure to isolate' episode may have more than one reason given where there were >1 unavailable single room with different reasons for their unavailability e.g. one single room occupied by an isolated patient and a second unavailable because of male/female bed availability.

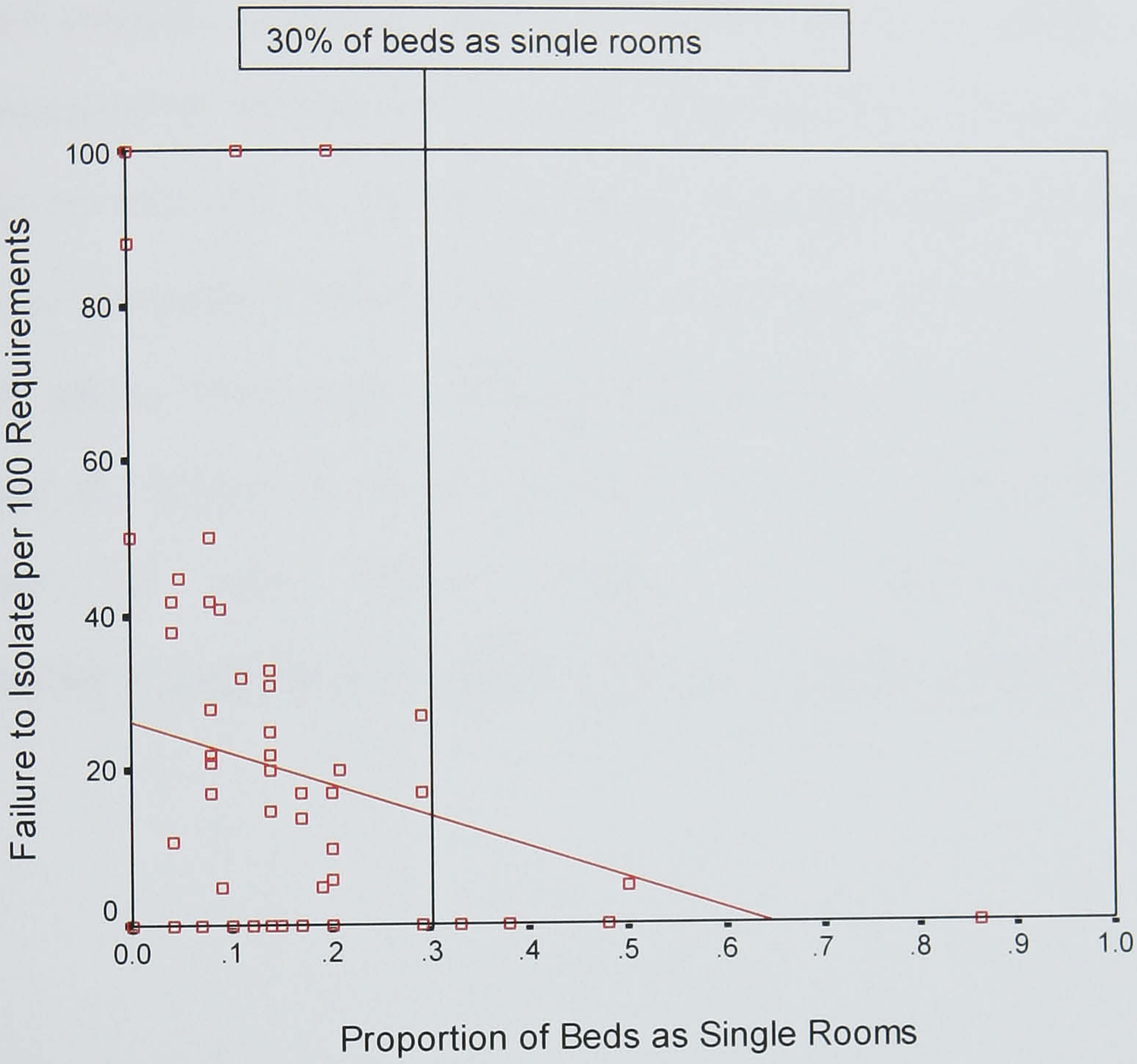
Table III Provision of single rooms, the demand for isolation facilities (expressed as number of requirements for isolation per 1000 patient days) and the number of 'failures to isolate' per 100 requests by clinical speciality.

Speciality	Total number of beds	Median number of single rooms per ward	Percentage of beds that are single rooms	Number of isolation requirements per 1000 patient -days	Number of 'failures to isolate' per 100 requests
Adult Intensive Care Units	28	2	29	8.6	16
Adult ENT	50	1	4	1.3	0
Cardiology	66	4	15	0.8	10
Cardiothoracic Surgery	74	4	11	1.7	5
Elderly Medicine	117	2	8	1.5	33
Gastroenterology	30	6	20	1.9	6
General Medicine	88	2	8	0.8	37
General Surgery	113	3	11	1.7	35
Haematology	14	14	100	1.7	0
Neonatal Units	50	1	8	0.3	14
Neurosciences	65	3	14	1.9	57[1]
Obstetrics/ gynaecology	78	6	23	0.2	0
Orthopaedics	70	2	10	1.7	11
Paediatrics (all)	125	2	26	2.2	7
Renal	23	2	9	4.1	5
Respiratory Medicine	73	2	12	2.9	32
Vascular Surgery	21	3	14	3.9	31
Others [2]	52	6	38	3.6	0

Notes

1. Includes Neuro HDU with 23 failures from 23 requests (no single rooms)
2. Dermatology, Breast care and ophthalmology

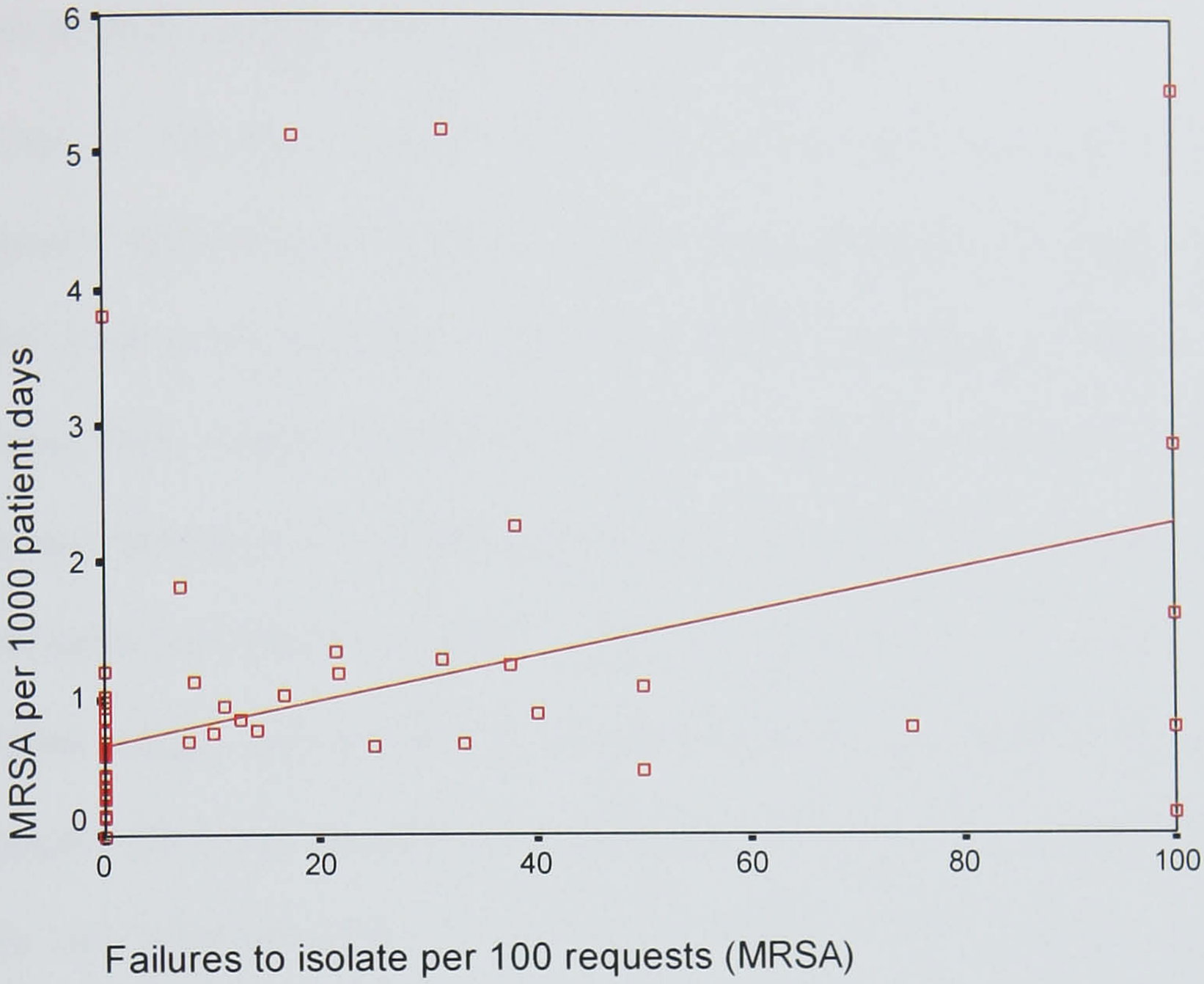
Figure 4 Scatter plot of 'failure to isolate' per 100 requirements and proportion of beds as single rooms (by ward) n = 60.



4.2. Prospective comparison of 'failure to isolate' patients with clinically ascertained MRSA and number of new clinical MRSA isolates by ward

The number of new MRSA isolates per 1000 patient days ranged from 0 to 5.48 (median 0.69, inter-quartile range 0.28 to 1.1) the data were heavily skewed towards the lower end of the scale. 'Failure to isolate' per 100 requirements for isolation (MRSA only) ranged by ward from 0 (58% of the wards) to 100 (8% of the wards) these data were also heavily skewed towards 0 (median 0, inter-quartile range 0 to 22.5). For both of the above, n = 60 wards. There was a statistically-significant correlation between the number of "failures to isolate" (MRSA only) per 100 requests and the number of new MRSA isolates per 1000 patient days (Spearman's ρ correlation coefficient = 0.596, $p < 0.001$, Figure 5).

Figure 5 Scatter plot of MRSA incidence per 1000 patient days and 'failures to isolate' (MRSA cases only) per 100 requirements by ward (n = 60)



4.3. Prospective observational study of MRSA acquisition comparing the contacts of index cases who were isolated with index cases who were not isolated

A total of 146 index cases were included in the study with 301 contacts (approximately two contacts per index case, range one to three). Two index cases had to be excluded from the analysis because of failure to recover isolates from frozen storage for typing, in one case ('failure to isolate' case with two contacts) the index case isolate could not be recovered and in the other case (successful isolation case with three contacts) none of the contact isolates could be recovered. The remaining 144 index cases had 296 contacts, 53 index cases were isolated with 119 contacts and 91 index cases were not isolated with 177 contacts. Seventy four contacts, 32 (27%) of index cases who were isolated and 42 (24%) of index cases who were not isolated, who were discharged or who were transferred after having an initial nasal swab on day 0 from which MRSA was not isolated, but before any further swabs could be taken, could not be included in the analysis.

The data pertaining to demographics and risk factors for this group are compared with those included in the analysis in Table IV. Contacts that could not be included were more likely to have an index case who was assessed as requiring isolation ($p = 0.04$, χ^2) and to have a dermatological condition ($p = 0.047$, χ^2). Fourteen index cases had no contacts that could be included in the analysis, thus 222 contacts (87 contacts of 50 isolated index cases

and 135 contacts of 80 not-isolated index cases) were included in the analysis.

Table IV Comparison of demographic and risk factor data between those contacts included in and those excluded from the analysis.

Demographic and risk factor data	Contacts included in the analysis n = 222	contacts not included in the analysis n = 74	Comments
Gender (%male)	61	49	NS
Age (mean)	71	68	NS
Index case isolated (%)	40	43	NS
Index case risk assessed as requiring isolation (%)	67	80	$p = 0.04$
Medical speciality (%)			
surgical	34	35	NS
medical	38	43	NS
elderly medical	22	12	NS
ICU/HDU	6	10	NS

Table IV (continued)

Demographic and risk factor data	Contacts included in the analysis n = 222	contacts not included in the analysis n = 74	Comments
Index case specimen type (%)			
fluid	1	4	NS
sputum	27	28	NS
wound swab	45	49	NS
blood culture	12	6	NS
urine	5	4	NS
tip	2	0	NS
other swab	9	5	NS
pus	1	0	NS
Index case has clinical infection (%)	40	30	NS
Index case with dermatology condition (%)	4	0	NS
Presence of intravascular catheters (%)	29	27	NS
Pressure ulcers (%)	1	0	NS

Table IV (concluded)

Demographic and risk factor data	Contacts included in the analysis n = 222	contacts not included in the analysis n = 74	Comments
Charlson co-morbidity index score < 3 (%)	78	74	NS
Surgery during this admission (%)	24	20	NS
Days from admission to day 0 (median)	6	7	NS
Presence of nasogastric tube (%)	6	5	NS
Number of ward transfers (median)	0	0	NS
Enteral feeding (%)	1	1	NS
Contact with dermatology condition (%)	3	9	$p = 0.047$[a]
Exposure to antibiotics (all classes, %)	45	42	NS

NS = Not significant ($p < 0.05$), a = Fisher's exact test.

MRSA was isolated from at least one nasal swab in 58 (26%) of 222 contacts that were included in the analysis. In 42 (19% of 222 contacts) of these cases MRSA was isolated from the first swab taken on day 0. Seventeen (8%) of these had an isolate that was indistinguishable by 'phage typing and PFGE from that of their index patient. The remaining 16 (7%) contacts from whom MRSA was isolated were initially negative for MRSA on day 0 and were considered to have acquired MRSA after day 0. Of these, 5 (2% of 222) acquired a strain of MRSA that was indistinguishable by 'phage typing and PFGE from that of their index patient. Index patients who were isolated had three contacts who acquired an indistinguishable strain of MRSA and index patients who were not isolated had two, the difference was not significant (p = 0.383, Fisher's exact test).

Three outcome measures were analysed for the contacts using univariate and multivariate analysis; firstly the identification of MRSA from any of the up to three swabs taken from each contact, described as 'MRSA positive at any time'. Secondly the identification of MRSA in a swab taken from a contact from whose initial swab at day 0, MRSA was not identified, described as 'MRSA-acquired'. Thirdly the same scenario as the second outcome where also the index and contact isolates were considered to be indistinguishable or closely related using PFGE (see 3.5.5.2), described as 'MRSA-acquired (isolate indistinguishable)'

Analysis of the risk factors for these three outcomes; 'MRSA positive at any time', 'MRSA-acquired' and 'MRSA-acquired (isolate indistinguishable)' are given in Table V (subject to univariate analysis) and Table VI (subject to multivariate analysis). Risk factors that were significant at $p < 0.2$ in univariate analysis were included in the multivariate analysis.

Table V Univariate analysis of risk factors for MRSA acquisition

	Outcome		
	MRSA positive at any time	MRSA acquired	MRSA acquired (isolate indistinguishable)
Risk Factor	significance in univariate logistic regression expressed as a *p* value		
Contact gender	0.645	0.916	0.401
Contact age	0.117[a]	0.696	0.870
Index risk assessed as requiring isolation	0.024[a]	0.222	0.174[a]
Index case isolated or not	0.819	0.361	0.457
Medical specialty	0.073[a] (surgical)	0.787	0.088[a] (medical)
Index case specimen type	0.115[a] (sputum)	0.661	0.498
Index – signs of clinical infection	0.348	0.166[a]	0.101[a]
Index – dermatology condition	0.115[a]	0.422	0.662
Presence of intravascular catheter	0.506	0.857	0.325
Pressure ulcers	0.776	0.627	0.791
Charlson co-morbidity index $\geq$ 3	0.732	0.708	0.891

Table V (concluded)

	Outcome		
	MRSA positive at any time	MRSA acquired	MRSA acquired (isolate indistinguishable)
Risk Factor	significance in univariate logistic regression expressed as a *p* value		
Surgery during this admission	0.956	0.913	0.838
Length of stay prior to day 0	0.064[a]	0.765	0.700
Presence of nasogastric tube	0.027[a]	0.255	0.573
No. of ward transfers prior to day 0	0.106[a]	0.692	0.109[a]
Enteral feeding	0.460	0.069[a]	0.829
Contact - dermatology condition	0.317	0.473	0.068[a]
Exposure to antibiotics (all classes)	0.073[a]	0.057[a]	0.151[a]
penicillins	0.768	0.030[a]	0.482
cephalosporins	0.942	0.902	0.671
aminoglycosides	0.685	0.382	0.706
macrolides	0.027[a]	< 0.001[a]	< 0.001[a]
trimethoprim	0.927	0.321	0.589
metronidazole	0.440	0.447	0.619
quinolones	0.001[a]	0.098[a]	0.073[a]

[a] significant at p < .2 and included in the multivariate model

Table VI Significant risk factors for MRSA acquisition after multivariate logistic regression analysis.

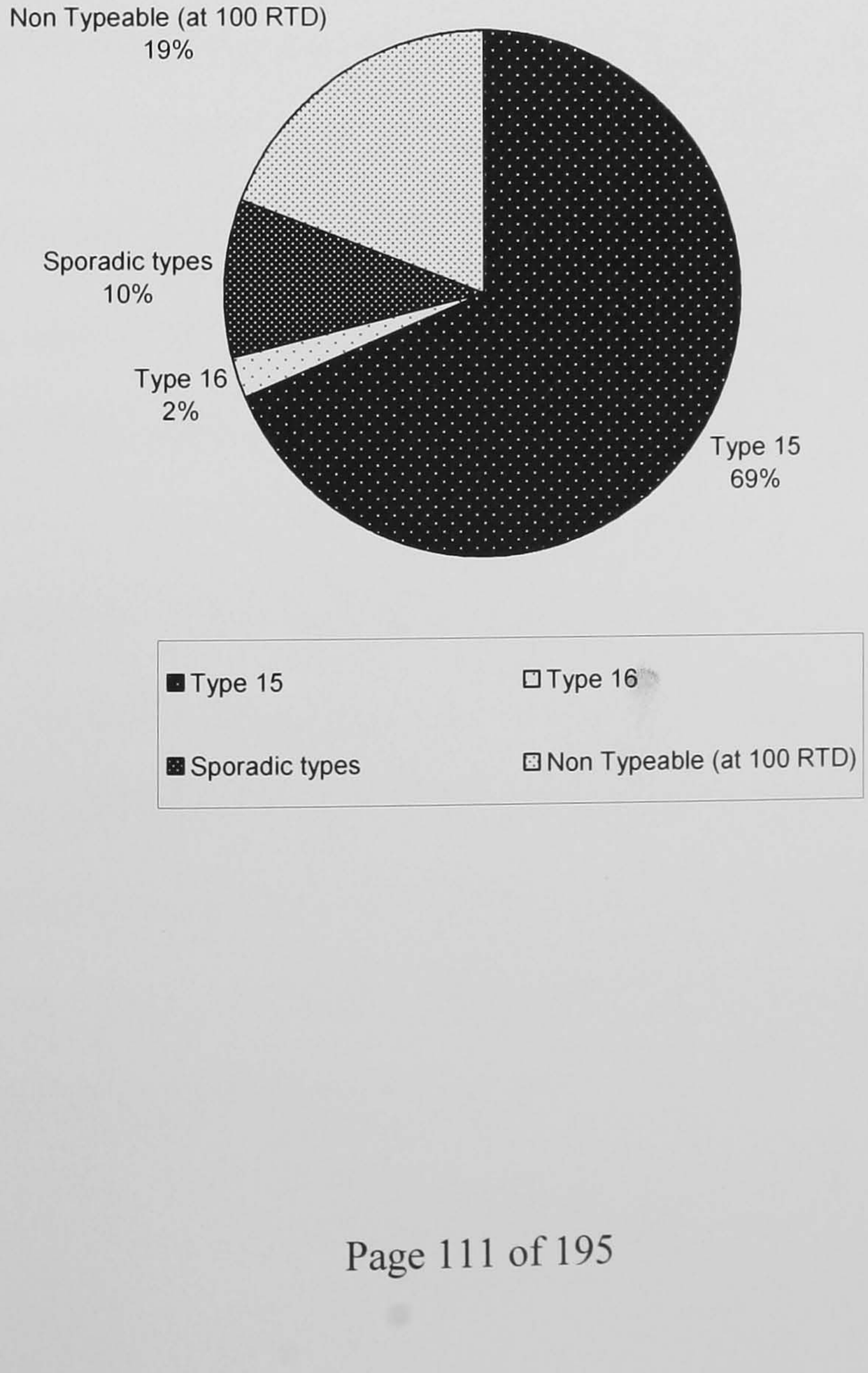
Outcome – MRSA positive at any time Model $\chi^2 = 30.11$, $p < 0.001$, $R^2 = 0.186$		
Risk Factor	exp b (95% CI)	*p*
Exposure to quinolones	4.31 (1.58 to 11.74)	0.004
Presence of nasogastric tube	4.07 (1.21 to 13.75)	0.023
Index case risk assessed as requiring isolation	2.35 (1.09 to 5.04)	0.029
Outcome – MRSA acquired Model $\chi^2 = 19.54$, $p = 0.003$, $R^2 = 0.208$		
Risk Factor	exp b (95% CI)	*p*
Enteral feeding*	30.54 (1.56 to 598.95)*	0.024*
Exposure to macrolides	7.14 (1.60 to 31.77)	0.010
Outcome – MRSA acquired, indistinguishable Model $\chi^2 = 20.72$, $p = .004$, $R^2 = .460$		
Risk Factor	exp b (95% CI)	*p*
Exposure to macrolides	21.51 (1.11 to 418.40)	0.043
Contact – dermatology condition	45.62 (1.30 to 1604.25)	0.035

*The model may be influenced by one case with high values for 'Cook's statistic' and 'DBeta' which indicate an undue influence on the model.

4.3.1. MRSA 'phage typing results

One hundred and sixty two MRSA isolates from 109 patients were 'phage typed, the relative proportions of the different 'phage types identified are shown in Figure 6 (n = 162 isolates). Analysis of 'phage types by broad hospital speciality showed that EMRSA type 15 was the predominant type in all specialities, with >50% of isolates belonging to this type.

Figure 6 The relative proportions of the different 'phage types identified



4.3.2. Pulse Field Gel Electrophoresis results

Figure 7 shows a dendrogram describing the degree of relatedness of the MRSA strains isolated from all patients in the study, both index cases and contacts, which were analysed using PFGE. This includes all cases where the index case and epidemiologically-related contact had MRSA strains that were indistinguishable by 'phage typing. The patients were numbered sequentially for the purposes of identification and for each contact the corresponding index patient number is given. The vertical line represents a cut-off point of 80% relatedness. This cut-off point represents approximately the definition of two strains being 'closely related' as described by Tenover *et al*[66] (see 3.5.5.2).

The dendrogram shows a high level of relatedness overall reflecting the very high proportion of strains that were classifies as EMRSA 15 using 'phage typing and the fact that the patients were all in the same hospital over a period of one year; however only index cases and their contacts were related specifically to each other epidemiologically.

Table VII Shows the index patients and their contacts as pairs and gives the percentage degree of relatedness of their MRSA strains and the corresponding definition according to the criteria of Tenover *et al*[66]. Again, this demonstrates the high level of relatedness of the dataset as a whole; the most common finding between pairs is one of 'closely related' whilst 'indistinguishable' and 'unrelated' are rare.

Figure 7 Analysis of PFGE profiles of MRSA strains from indexes and contacts

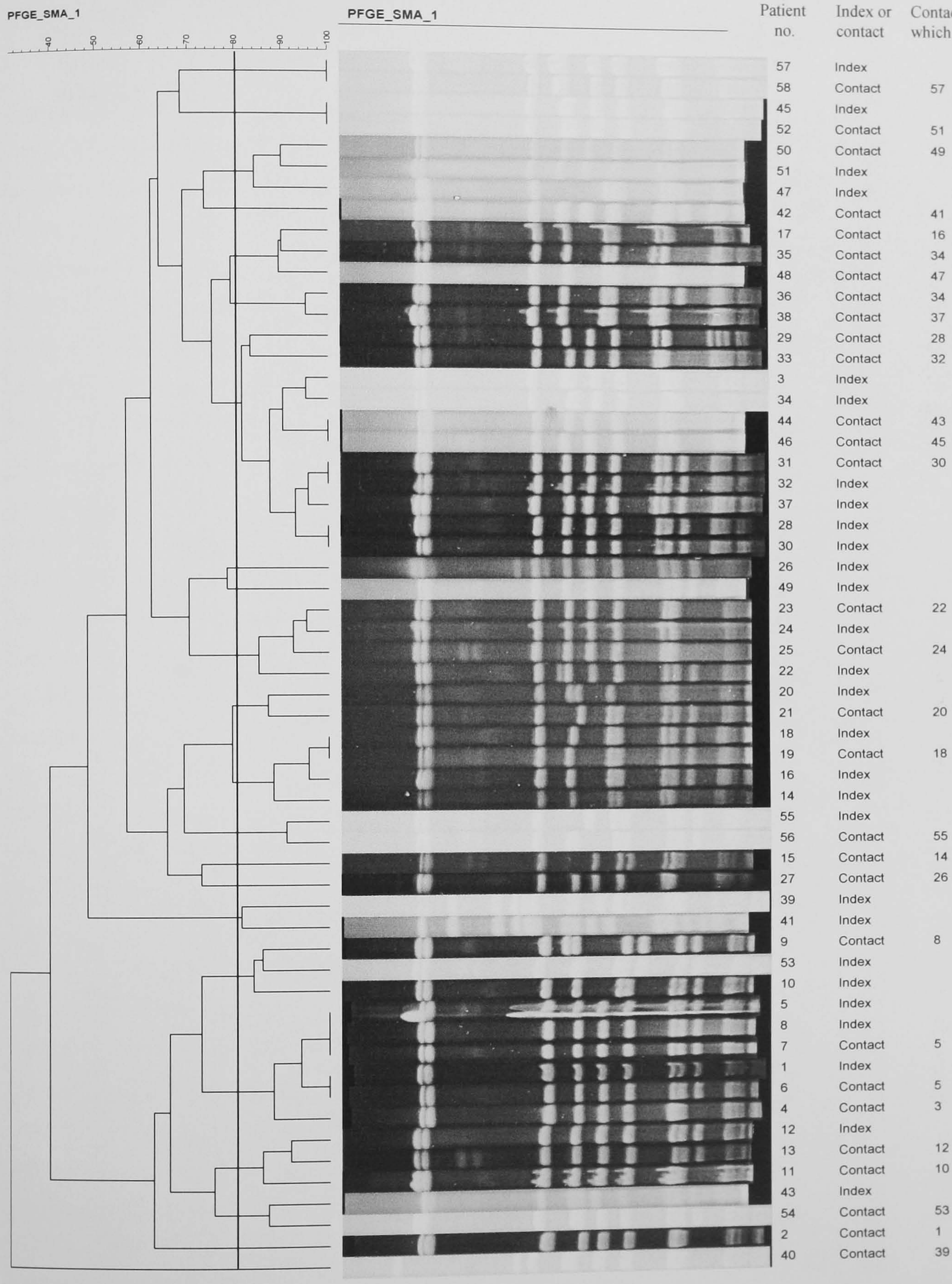


Table VII The percentage degree of relatedness of MRSA strains for each index case and their corresponding contact with the description of their relatedness from Tenover *et al*[66].

Index case patient number	Contact patient number	Percentage degree of relatedness (%)	Description of relatedness
1	2	85.12	Closely related
3	4	88.89	Closely related
5	6	99.99	Indistinguishable
5	7	99.99	Indistinguishable
8	9	72.73	Possibly related
10	11	85.72	Closely related
12	13	99.99	Indistinguishable
14	15	69.57	Unrelated
16	17	95.24	Closely related
18	19	99.99	Indistinguishable
20	21	86.96	Closely related
22	23	95.24	Closely related
24	25	94.74	Closely related
26	27	70.00	Possibly related
28	29	88.00	Closely related
30	31	95.65	Closely related
32	33	95.24	Closely related
34	35	84.21	Closely related
34	36	60.00	Unrelated
37	38	70.00	Possibly related
39	40	66.67	Unrelated
41	42	64.29	Unrelated
43	44	88.89	Closely related
45	46	84.21	Closely related
47	48	88.89	Closely related
49	50	86.96	Closely related
51	52	84.21	Closely related
53	54	63.64	Unrelated
55	56	90.01	Closely related
57	58	99.99	Indistinguishable

5. Discussion

The NHS in England and Wales is currently in the middle of an unprecedented programme of hospital building with approximately 110 new hospitals being built at a cost of approaching £30 billion. [286] The question of the size and nature of the need for isolation facilities has never been timelier.

Patient isolation to limit the spread of nosocomial pathogens is a mainstay of infection prevention and control programmes worldwide. However, the true efficacy of isolation as a control measure for some organisms, in particular MRSA, remains uncertain. [197 198] Clearly, the effectiveness of isolation in preventing the transmission of HAI pathogens will, at least in part, be governed by the supply of and the demand for single rooms.

This study demonstrates a major mismatch between demand for and supply of isolation room facilities. Approximately one in five requests for patient isolation was not met during this 12-month period. There are no other published reports in the literature that have examined the use of single rooms using this method but those that have conducted point-prevalence surveys of the use of single rooms have reported findings that were similar to those in this study, *i.e.* single rooms that were occupied by patients who were not suffering from an infection, while patients who are deemed to carry a risk of transmitting infection remain on open wards. [234 235] In addition, those studies that have examined the use of isolation rooms in infectious disease facilities have also found a mismatch between their intended and actual

use. [232 233] The extent to which these findings reflect the situation in other UK hospitals is not known, however the available evidence and anecdotal knowledge suggests that they are unlikely to differ markedly in other comparable large NHS hospitals.

Requests for isolation of patients for the purposes of infection control are made as part of a risk assessment of the likely transmissibility of pathogens, in line with standard UK practice. The main driver for the isolation of a patient for the purposes of infection control in this study was MRSA carriage/infection, which accounted for almost half of all such requests. The incidence of MRSA infection in the study hospital, as judged by national surveillance of MRSA bacteraemia, is similar to that in other large, specialist hospitals in England. [277] The prevalence of MRSA, at approximately 40% of all *S. aureus* isolates, is also similar to comparable hospitals. The absence of any previous national guidance for, or published data on, the availability of isolation rooms also hinders comparison of the capacity of single rooms locally with that in other NHS hospitals; however, approximately 17% of beds in the study hospital were in single rooms, and according to NHS Estates 'the NHS rarely provides more than 20% single rooms in its hospitals'. [229] The lack of progress over time in increasing the proportion of beds that are single rooms in hospital buildings is illustrated by the percentage of beds provided in single rooms being almost identical in the three main hospital buildings, despite a gap of more than 100 years between construction of the

oldest (*c* 1880) and newest (1998); although the oldest of these has undergone some refurbishment over time.

Comparison of isolation facilities by clinical specialty demonstrated a significant variation in the provision of, demand for and availability of single rooms. 'Failure to isolate' was consistently high in wards for General Medicine, Surgery and Elderly Medicine. By contrast, in Obstetrics and Gynaecology and Paediatrics, where provision of single rooms was relatively high, the demand for isolation for the purposes of infection control was very low and thus 'failures to isolate' were rare. The significant inverse correlation between the proportion of single rooms and increased 'failure to isolate' is unsurprising. Notably, in only one case where a ward had $\geq$ 30% of its beds provided in single rooms, there was an instance of 'failure to isolate'. This may support the current NHS guidance on the provision of single rooms, though this is limited to design specifications for new hospitals and departments only, that recommends at least 50% of the total beds should be provided in single rooms. [227] Interestingly, this study identified that the great majority (81-88%) of single rooms were being occupied for reasons other than infection control requirements.

The capacity to isolate a patient on request may be influenced by a number of factors, including the proportion of beds that are in single rooms, the bed occupancy rate, the policies and protocols for risk assessment that are in

place (*e.g.* whether patients with MRSA colonisation are isolated), the use of mixed-sex wards and the prevalence of organisms/conditions requiring isolation. The majority of requests for patient isolation in this study related to either MRSA colonisation/infection or *Clostridium difficile* diarrhoea. This reflects the high endemic level of these pathogens in UK hospitals. It is important to note that in the study hospital routine screening for MRSA carriage was not practised at the time of these studies. Instead, patients were isolated who were identified as infected or, sometimes, simply colonised with MRSA through clinical sampling, according to risk assessment as recommended in the UK guidelines that were extant at the time of the study [189]. It is therefore conceivable that if widespread screening was carried out this would identify a larger number of patients colonised with MRSA, which would increase the size of the gap between demand for and supply of single rooms. For the majority of microorganisms and infections the proportions of 'failures to isolate' were consistently around 20%, the only exceptions being microorganisms/infections for which isolation is considered mandatory (for example, untreated pulmonary tuberculosis), and those occurring predominantly in children (for example, rotavirus). The length of time that 'failure to isolate' persisted varied markedly; although most cases were resolved within 5 days, a small number lasted 2-3 weeks. The reasons for these longer durations include the need for specialist (*e.g.* high dependency) care, which was not available in isolation in a single room. Occasionally, the long duration of 'failure to isolate' may be exacerbated by

an inability to review cases daily to determine if the infection-control risk assessment has changed.

In the event of 'failure to isolate', patients are managed in open areas of wards and departments using modified contact (barrier) precautions. Precise patient placement depends on risk assessment and the configuration of the ward or department. Subsequent risk of microorganism transmission is multi-factorial and hard to quantify. This risk is expressed as the number of patient days of exposure (assuming 100% bed occupancy). These data suggest that even if only a small proportion of exposures lead to nosocomial infection the consequences in terms of morbidity, mortality and healthcare costs will be significant.[287] The finding that there was a significant correlation between failing to isolate patients who had MRSA isolated from clinical specimens and the incidence of MRSA identified from clinical samples needs to be interpreted with care. The epidemiology of MRSA is complex and influenced by many risk factors related to both individual patients and the clinical setting. Correlation does not imply, and should not be interpreted as implying, cause and effect. Increased 'failure to isolate' could lead to higher incidence of MRSA colonisation and/or infection. It is also plausible that increased MRSA prevalence could lead to an increase in 'failure to isolate'. It is also possible that neither of these scenarios is true and that these data and this apparent relationship are confounded by one or more unknown factors. In particular antibiotic use has

been shown to affect MRSA infection rates at the ward or unit level. [120] It was intended to collect data on antibiotic usage by ward as part of this aspect of the study. Unfortunately, despite being apparently feasible in planning, it was not possible to make use of the available pharmacy data in this way because of problems with attributing antibiotic use to wards and departments as opposed to prescribing clinicians. In addition, non-parametric correlation was used because the data were unsuitable for linear regression.

It was possible to categorise broadly the reasons for 'failure to isolate' patients. Some reasons for failing to isolate patients were clearly structural and related to the design and use of available facilities *e.g.* wards and departments designed and built (or inherited) without any single rooms. The use of mixed-sex wards also had a negative impact; on 26/185 (14%) of 'failure to isolate' occasions a single room was unavailable because of the gender of its occupant and consequent inability to transfer them to the open ward. Attempts to reduce mixed-sex occupancy in the NHS have been mainly restricted to segregation of males and females within wards and departments and the provision of separate bathroom and toilet facilities, which has little bearing on usage of single rooms. [288 289]

The availability of single rooms is affected by cases already isolated with transmissible pathogens, and those in single rooms for other clinical reasons

such as terminal care or the appropriate management of disturbed or disruptive patients. More than one third of cases of 'failure to isolate' were due to the former. A broad category of 'failure to isolate' reasons relate to the perceived needs of, or risks to, the index patient *e.g.* the potential for physiological or psychological deterioration, or the need for care that cannot be delivered in isolation. These assessments by clinical staff need to be considered seriously as there is evidence that patients placed in isolation can suffer both psychological harm [246-250] and increased adverse events. [254] Patients may also require high-dependency or other specialised care which militates against isolation needs.

The necessity for, and the efficacy of, isolation for the prevention of transmission of organisms that are spread via the airborne route is based on a strong theoretical rationale. Airborne transmission of organisms such as *Mycobacterium tuberculosis* and varicella zoster virus has been demonstrated [220] and, while controlled trials would certainly be rejected on ethical grounds, using isolation, ideally with controlled ventilation, to prevent such transmission is universally accepted and uncontroversial. This is not the case for organisms spread by contact; the finding in this prospective cohort study that there is no significant difference in the acquisition of genetically indistinguishable or closely related MRSA in adjacent contacts of index cases who were isolated and those who were not isolated adds to the

considerable debate about the efficacy of isolation in a single room in preventing pathogens spreading by this route, particularly MRSA.

It has been established that isolation in a single room is not necessarily a benign practice. [246-256] It is imperative from an ethical perspective, therefore, to establish whether the practice is effective in preventing the transmission of epidemiologically-important organisms.

There are no other published studies that have prospectively examined MRSA transmission from an index patient to a cohort of adjacent contacts in this way. The only published study that is methodologically similar is that of Jernigan *et al.* [290] This study was included in the systematic review by Cooper *et al.* [197] and described the use of contact precautions in controlling an outbreak of MRSA in a neonatal intensive care unit (NICU). This study identified transmission using judgements based on the temporal and geographical relationships between putative index cases and cases of acquired MRSA. The authors reported a 16-fold difference in MRSA transmission from index cases who were isolated and those who were not isolated (RR 15.6, 95% CI 5.3 to 45.6, $p < 0.0001$). These findings appear to support the use of contact precautions (including isolation in a single room) in preventing the transmission of MRSA but they may also be explained by regression to the mean as the majority of transmissions occurred at the beginning of outbreak (8 out of 15 in the first month of a five-month outbreak)

and a number of additional measures were introduced to quell the outbreak during this period. Other than this study, which they considered to provide only weak evidence of the efficacy of isolation, Cooper and colleagues identified that the overwhelming majority of published reports that claim that isolation is effective in preventing MRSA transmission are either, reports of outbreaks in which multiple uncontrolled interventions have apparently terminated the problem frequently with unplanned, retrospective analyses or, at best. prospective 'before and after' intervention studies. Of the studies they reviewed and considered to provide more robust evidence of efficacy (six in total) there was a mixture of outcomes with four supporting the efficacy of isolation and two not. It is also important to note that only three of these studies primarily used isolation in a single room; the remaining three were studies of isolation wards.

Of the studies included in the subsequent systematic review by Loveday *et al.* [168] none addressed the impact, at the individual patient level, of isolation. Reviewing the studies that have been published since the period covered by these reviews identified one study by Bracco and colleagues [276] set in an ICU that found a lower incidence of acquired MRSA in occupants of single rooms than those in open bays. As well as questioning the validity of these findings, due to the differences in the two groups being studied, it is also difficult to identify their applicability to practice as, normally; it is the potentially infectious individual that is placed in the single room as opposed

to those at risk of acquisition with the exception of those patients placed in protective isolation, this latter group of patients being such a small and unusual group that their management has little or no bearing on the wider debate about isolation.

The findings of this study support those of Cepeda and colleagues [270] who found that isolation in a single room of patients with MRSA did not affect the rate of MRSA acquisition in two ICUs. Although the study of Cepeda and colleagues was set in ICU and didn't attempt to identify direct MRSA transmission it is similar to this study in one important aspect; it examined the specific impact of isolation in a single room without other simultaneous interventions.

There are a number of potential explanations for the finding that isolation of index cases did not significantly affect the acquisition of genetically indistinguishable isolates of MRSA by their contacts when compared with the contacts of index cases who were not isolated. Although an airborne component to MRSA transmission has been suggested by some studies [155-159] the primary route of transmission is via direct or indirect contact and it is plausible that the isolation of individuals in single rooms does not prevent transmission by this route. Although use of a single room is advocated as a component of contact precautions it is only one of the interventions that make up these precautions and its individual contribution to transmission

may be relatively small when compared to the other components such as hand hygiene, equipment and environmental hygiene and the use of personal protective equipment *e.g.* gloves and aprons. The use of single rooms may be considered as a measure to improve compliance with the above measures, through raised awareness of the status of the isolated patient; however there are no studies to substantiate this and compliance with contact precautions is reported to be suboptimal at best and very poor at worst. [240-245] If compliance with contact precautions was equally poor during this study it could provide another explanation for the apparent lack of effect associated with isolation. Were that the case, however, it could be argued that there would have been higher transmission rates in contacts of index cases, whether isolated or not.

It is plausible that isolation in a single room of a patient in whom MRSA has been identified protects patients other than those who have been in the index case's immediate vicinity. If transmission occurs primarily via the hands of healthcare workers then the work patterns of the healthcare workers may influence who is placed at risk of MRSA acquisition *i.e.* those patients identified as 'contacts' in this study may, in some cases, be cared for by different healthcare workers than the index case; in addition other patients who were not adjacent to the index case could have been cared for by the same healthcare workers thus placing them at increased risk in the event of non-compliance with infection control precautions. This possibility

could explain why studies such as that by Gastmeier *et al.* [267] have identified an overall reduction in MRSA incidence when patients with MRSA are placed in single rooms.

Another partial explanation of the apparent lack of transmission of MRSA from index cases to contacts in either scenario could be that 19% of the potential contacts were already colonised with MRSA on entry to the study (at day 0); given that these individuals were presumably at higher risk for MRSA acquisition, they may have been those who were most likely to have acquired it from their contact, if not already colonised. This finding and the fact that, at some point, one in four (26%) of all the contacts in this study had a nasal swab that yielded MRSA following culture reflects the endemic nature of MRSA and its high prevalence in the study setting. A recently published study of MRSA prevalence in residents of nursing homes in the same geographical area (Leeds UK) found a remarkably similar prevalence of MRSA nasal colonisation (22%). [291] It is unclear as to whether the prevalence of MRSA in this particular cohort of patients, *i.e.* those adjacent to patients in whom MRSA has been identified through clinical specimens, was higher than would be found in a bay of patients selected at random in which there were no known MRSA cases. It is, however, likely that this prevalence figure is an overestimate of the prevalence figure for the hospital as a whole as there are varying levels of MRSA incidence, as identified by the number of cases identified from clinical samples, among the different

clinical specialities. Therefore the sampling for this study was largely concentrated in those clinical specialities with the highest prevalence of MRSA rather than the average for the whole hospital.

The results of the PFGE analysis demonstrate that there was a high level of relatedness among the majority of the strains of MRSA from both index cases and their epidemiologically related contacts, reflecting the very high proportion of strains that were classifies as EMRSA 15 using 'phage typing and the fact that the patients were all in the same hospital. For the purposes of the analysis, index and contact isolates of MRSA were considered to be related if they met the criteria for either 'indistinguishable' or 'closely related' as described by Tenover *et al* [66]. Given that, it is surprising to note that in a number of instances, the isolate derived from an apparent contact was unrelated to the relevant index case. Thus, detailed molecular typing shows that these apparent contact cases are, in fact, index cases in their own right. This adds a layer of complexity to the epidemiology presented in this thesis since the apparently simple epidemiological picture obtained using widely-applied typing tools may be misleading when a more discriminatory analysis is applied. It also follows from this that any measure of the spread of MRSA obtained using relatively simple typing is likely to be an overestimate of the ability of this bacterium to spread through this cohort f patients. This highlights the need to use typing tools that have a high

degree of discrimination when studying bacterial strains that are closely related.

The risk factors for the acquisition of MRSA identified in this study add to the evidence that supports exposure to antibiotics in general and specific antibiotic classes in particular as a significant predictor of MRSA acquisition. Exposure to quinolones was a significant risk factor for the outcome 'MRSA at any time', *i.e.* including those contacts whose day 0 samples were positive for MRSA. Contacts who acquired MRSA, whether genetically related to that of their index case or not, were more likely to have received a quinolone than those who didn't acquire MRSA but this did not reach statistical significance. These findings reinforce those of a number of earlier studies that exposure to quinolones is an independent risk factor for MRSA acquisition. [76 82 120 122 125 128-132]

In this study, exposure to a macrolide was a significant risk factor in univariate analysis for all outcomes and in multivariate analysis it remained an independent risk factor for acquired MRSA and acquired MRSA where the isolate was indistinguishable from that of the index case. Exposure to macrolides has only been reported rarely as a risk factor for MRSA acquisition, Onorato *et al.* [100], in a multivariate analysis, identified that exposure to one or more of a group of antibiotics that included macrolides was a risk factor for MRSA acquisition in patients infected with the Human

Immunodeficiency Virus (HIV); however, they did not analyse the antibiotic classes separately and it may not be possible to extrapolate data from HIV patients to other populations. An older study (1993) by Shimada and colleagues [85] identified exposure to macrolides as well as aminoglycosides, tetracycline and carbapenems as being independently associated with MRSA surgical wound infection. This study did not attempt to identify risk factors for acquired MRSA colonisation.

In the case-control study by Graffunder and Venezia [82], macrolide exposure, as well as exposure to levofloxacin, was found to be an independent risk factor for nosocomial MRSA infection compared with MSSA infection. Unlike levofloxacin, however, macrolide exposure was not significant in a second model that included the number of grams administered.

Muller *et al.* [120] examined the relationship between antibiotic use and the incidence of MRSA at the ward or unit level using an ecological approach. They found that the use of all classes of antibiotic, including macrolides ($p = 0.004$) was independently associated with higher MRSA incidence when controlled for 'colonisation pressure' and type of clinical speciality. The authors were unable to determine a hierarchy of risk among the different antimicrobial classes and while there was a linear dose-effect relationship between levels of usage and MRSA incidence with some classes of antibiotics (quinolones and cephalosporins); this was not true for macrolides where the effect tended to plateau.

Whereas specific mechanisms that may contribute to the impact of exposure to quinolones on MRSA incidence have been described, [131 132 134] this is not the case for macrolides; however, in common with quinolones, macrolides do achieve high skin concentrations [20] so similar mechanisms could be involved. There are other antibiotics that also achieve high skin concentrations *e.g.* tetracyclines and lincosamides but these are used much less frequently. It is possible that the association between macrolides and MRSA colonisation may be due to the fact that macrolides are excreted onto the skin which, in combination with their poor activity against MRSA means that they create a selective pressure that makes MRSA colonisation more likely to follow initial contact with the organism from, for example, cross-infection from another patient, member of staff or the inanimate environment. This effect may be less likely in other antibiotics that achieve high skin concentrations where such antibiotics are more active against MRSA *e.g.* tetracyclines. Further research is needed into any such potential mechanisms for this association.

Overall, the results of this study reinforce the importance of exposure to antibiotics in the spread and acquisition of MRSA, quinolones are already strongly established as a risk factor but these results add to the smaller body of evidence that exposure to macrolides may also predispose to MRSA acquisition.

The finding that those index cases who were identified by the infection control nurse or doctor as 'requiring isolation' was independently a risk factor for the outcome of MRSA from any of the up to three swabs taken from each contact, described as 'MRSA positive at any time' but not for the outcomes associated with the acquisition of MRSA is difficult to interpret. In a situation where there are insufficient single rooms to isolate all cases of MRSA (whether colonised or infected), in addition to other epidemiologically important organisms *e.g. Clostridium difficile*, infection-control nurses and doctors are frequently required to decide if isolation is required using risk assessment. Although specific systems for risk assessment have been proposed, both for all isolation cases [236] and for MRSA specifically, [237-239] most risk assessments are not done systematically, as was the case during this study. Such risk assessments were based on criteria such as whether the index case had a clinical infection, whether there was an opportunity for increased dissemination of the organism *e.g.* exfoliating skin conditions, open wounds, respiratory infections or colonisations with coughing and expectoration and on the consequences for adjacent patients should transmission occur. This latter factor would, for example, make isolation of an MRSA patient more likely on a ward where complex surgery was undertaken *e.g.* orthopaedic implant surgery. If these risk assessments were valid then it is reasonable to consider 'that those index cases who were risk-assessed by the infection control nurse or doctor as 'requiring isolation'

would pose a significantly greater risk for MRSA transmission; however this factor was only significant, both in univariate and multivariate analysis, for the outcome 'of MRSA from any of the up to three swabs taken from each contact, described as 'MRSA positive at any time''. It is difficult to identify a plausible mechanism for this apparent relationship; it could be proposed that, in some cases, MRSA was acquired from the index case prior to that individual being identified as having MRSA but although 17 contacts who had MRSA identified from a swab taken on day 0 had an isolate that was indistinguishable from that of the putative index case, it is not possible to identify which of these individuals acquired MRSA from the other or whether both have acquired MRSA from another, unidentified source.

Although 'presence of a nasogastric tube' has been identified previously as a risk factor for MRSA acquisition [83 87 88] this has been only in a univariate analysis, this is the first report of the presence of a nasogastric tube as an independent risk factor using multivariate analysis; however there are reports of enteral feeding as an independent risk factor [82 99] and it is likely that at least some of the patients identified as receiving enteral feeding will have done so via a nasogastric tube. It may be that previous studies that identified enteral feeding as a risk factor were confounded due to the nasogastric tube being the risk factor rather than the feeding *per se*. It is plausible for nasogastric tubes to present an increased risk of MRSA acquisition, placed as they are in a major site for colonisation by MRSA, it

may be that the presence of a foreign body in the nare increases the risk of adhesion and persistence of MRSA and, possibly, MSSA.

The finding that 'enteral feeding' was an independent risk factor for acquired MRSA, though supported by previous studies as described above, needs to be interpreted with caution. The number of contacts who had enteral feeding was very small (2/222) and detailed examination of the statistical model strongly suggests that one case had an undue influence on the overall model. It is very likely that this finding is a statistical anomaly.

Damage to skin integrity due to, for example pressure ulcers or dermatological conditions is recognised as a risk factor for MRSA acquisition and persistence [74 83 97 99 100] and the results of this study support this in finding that a contact suffering from a dermatological disorder such as eczema or psoriasis for example was an independent risk factor for them acquiring MRSA where the isolate was indistinguishable from that of the index case; again the number of cases is very small and though there is no statistical reason to suspect that the model is invalid, the result should be interpreted with caution.

There are some limitations to the study to consider; because of the nature of the study design, in effect a 'natural experiment', the index cases were not randomised to isolation or no isolation, this creates a risk of selection bias in

the study. To overcome this, data on potential confounders, identified from the literature, were collected and included in the analysis and regression analysis used to control for their potential effects. [292 293]

Performance bias would describe differences in the care or management of patients included in the study, some aspects of 'performance' *e.g.* antibiotic prescription and length of stay, were included in the data collection and analysis, however others such as bed occupancy and workload and in particular the quality of the compliance with isolation precautions were not. It is a weakness of the study that there was no measure of the compliance with contact or barrier precautions for either those index cases who were isolated in single rooms or those who were managed using contact precautions in an open bay; however such observational study was beyond the scope and the means of this study. It is likely from the literature and from anecdotal experience that compliance was at best sub-optimal and very likely poor. It is interesting to note that despite this likelihood the proportion of directly attributable MRSA transmissions was very low.

Another important weakness is the lack of information regarding what has been described as 'colonisation pressure' [95] (*i.e.* the proportion of patients in the ward who are known to be colonised with MRSA). The study setting did not, at the time of the study, practise admission screening routinely on any patients, so it is likely, and borne out by the numbers of MRSA results

identified at day 0, that there were patients on the ward with undetected MRSA colonisation. There is however no reason to suspect, given that the study was prospective with contemporary controls, that this would result in a systematic bias.

Detection bias describes a situation in which the assessment of the outcome of the study is conducted in an unequal or biased manner between the two groups being studied. The outcome of this study was MRSA acquisition and it is possible for two reasons that some cases of MRSA acquisition were not detected during this study; firstly only nasal swabs were taken and these were plated directly onto agar without enrichment and secondly the maximum follow up period was fourteen days (in practice, only a small proportion of contacts remained in hospital for fourteen days and follow up was usually until discharge or transfer). The use of nasal swabs without enrichment was a pragmatic choice based on anecdotal experience of point-prevalence surveys, there is a lack of high-quality evidence on the optimal strategy for identification of MRSA colonisation [163] however nasal screening alone can identify > 90% of colonised individuals [279] and is considerably less intrusive than swabbing multiple sites which may have caused patients to refuse their consent. Again there is no reason to suspect that this approach would have caused a systematic bias.

There is a possibility that the study may be prone to attrition bias, *i.e.* differential loss to follow-up between the two groups. There were a number of contacts who could not be followed up after their initial day 0 swab because of discharge or transfer, these were evenly distributed between the two groups but there were more contacts, who could not be included in the analysis, whose index case was risk-assessed as needing isolation and also more who had dermatology conditions. It is possible that some of these could have gone on to acquire MRSA but importantly this group (*i.e.* those with additional risk factors for acquisition) were evenly distributed between index cases who were isolated and those who were not.

6. Conclusions and recommendations

6.1. Conclusions

There is a general and anecdotal perception, as demonstrated by the description from the only UK guidance on isolation, of a recommendation to isolate as 'a council of perfection', that 'failure to isolate' is significant problem in NHS hospitals. This is the first study to quantify such failure prospectively. The results are disturbing and, if extrapolated to the NHS as whole, imply a systematic failure to apply what is considered 'standard practice' in the control of HCAI. From the available evidence, and from anecdotal knowledge, there is little reason to believe these findings would not be broadly similar in other NHS hospitals. Newer hospitals with increased numbers of single rooms are being built but it will be many years before the overall provision of single rooms is greatly improved beyond the current situation.

There is no doubt that, under the current circumstances, many patients are being placed at some, albeit unquantifiable, risk of exposure to pathogens. What is apparent from these data is that the demand for isolation in a single room facility in hospitals is highly varied and the overall proportion of beds as single rooms in a hospital is unlikely to give sufficient detail as to the adequacy of provision. NHS hospitals need to consider the need for, and provision of, single rooms on the basis of specialities and even individual units.

Debate continues as to the optimum provision of accommodation in single rooms in new hospitals and major refurbishments but the current guidance that at least 50% of beds should be provided as single rooms will, given these results, eventually go some way to closing the gap between demand and provision.

There is an inherent tension between the finding that there is a significant correlation between failing to isolate patients risk-assessed as requiring isolation and clinical MRSA incidence, and the relative lack of MRSA transmission from index cases who were not isolated to their immediate neighbours. Correlation does not demonstrate cause and effect and it should not be inferred from it, there is more than one plausible explanation for this finding, not least that increasing numbers of cases of MRSA may lead to 'failure to isolate' as opposed to being caused by it.

Evidence for the effectiveness of isolation in a single room in preventing the spread of organisms spread primarily by the contact route is limited and based in large part on unplanned and methodologically-weak studies. This study found, in a cohort of patients in the immediate vicinity of index cases from whose clinical specimens MRSA had been identified that there was little apparent transmission of MRSA and that such transmission was not decreased through isolation of the index patient. These findings do not in

themselves prove that isolation is ineffective *per se* as there are other plausible explanations for its potential effect in reducing transmission; nevertheless they make a significant contribution to the debate.

6.2. Recommendations

NHS hospitals should review their provision of single rooms in light of these findings and consider how their provision on a speciality and individual unit basis can be best managed to meet demand.

Those responsible for the commissioning and design of new hospitals and major refurbishments should take account of these findings which support current recommendations that a minimum 50% of beds should be provided as single rooms. In addition, consideration should be given to the potential demand for isolation in individual specialties and units and, where necessary, additional isolation capacity should be provided.

Further research is needed into the effectiveness of isolation in a single room in the prevention of MRSA transmission. Specifically, a large, randomised intervention study of isolation *vs.* standard or contact precautions (without isolation in a single room). Such a study would need to be randomised at the ward or unit level and would need to include data collection on potential confounding variables, in particular: antibiotic usage, workload and the quality of the standard and isolation precautions used.

Given the lack of data to demonstrate the efficacy of isolation in this context such a study would appear to be ethically acceptable; however the current climate of raised public concern about HCAI could present significant difficulties.

7. Publications and presentations

Wigglesworth NA & Wilcox MH (2006) Prospective Evaluation of Hospital Isolation Room Capacity. *Journal of Hospital Infection*; 63, 156-161

Wigglesworth NA & Wilcox MH (2006) *How Does Success or Failure to Isolate Patients Affect the Control of Meticillin Resistant Staphylococcus aureus?* Poster Presentation, 6th International Conference of the Hospital Infection Society. Abstract no. P4.10

Prospective evaluation of the effects of isolation on the transmission risk for MRSA, Wigglesworth NA & Wilcox MH *in preparation*

8. List of abbreviations used in the text

CA-MRSA	Community acquired MRSA (See MRSA)
CDC	Centers for Disease Control and Prevention
CI	(95%) Confidence intervals
DNA	Deoxyribonucleic acid
ENT	Ear, nose and throat
ESBL	Extended spectrum β-lactamase
EUR	Euro (€)
GISA	Glycopeptide intermediately resistant *Staphylococcus aureus*
HAI	Hospital acquired infection
HCAI	Healthcare-associated infection
HDU	High dependency unit
ICU	Intensive care unit
LGI	Leeds General Infirmary
LIPS	Lewisham Isolation Priority System
LOS	Length of stay
MDRO	Multi-drug resistant organism
MIC	Minimum inhibitory concentration
MLST	Multi-locus sequence typing
MRSA	Meticillin resistant *S. aureus*
MSSA	Meticillin sensitive *S. aureus*
NHS	National Health Service
OR	Odds ratio
PCR	Polymerase chain reaction
PFGE	Pulse field gel electrophoresis
PVL	Panton – Valentine leukocidin
RCT	Randomised controlled trial
RR	Relative risk
RTD	Routine test dilution
SCC*mec*	Staphylococcal chromosomal cassette
TE	TRIS-HCL, EDTA (buffer)
TEN	TRIS-HCL, EDTA, Sodium Chloride (buffer)
TISA	Teicoplanin intermediately resistant *S. aureus*
USA	United States of America
USD	United States Dollar ($)
UK	United Kingdom
VAP	Ventilator associated pneumonia

List of abbreviations concluded

VISA	Vancomycin intermediately resistant *S. aureus*
VRE	Vancomycin resistant enterococci
VRSA	Vancomycin resistant *S. aureus*

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Appendix A:

Centers for Disease Control and Prevention (CDC) grading of evidence to support recommendations[192]

- Category 1a. Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiological studies.

- Category 1b. Strongly recommended for implementation and strongly supported by certain experimental, clinical or epidemiological studies and a strong theoretical rationale.

- Category 1c Required for implementation, as mandated by federal or state regulation or standard. [The UK equivalent is to operate within EU or UK Health & Safety Legislation].

- Category 2. Suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale.

- No recommendation. Unresolved issue. Practises for which insufficient evidence exists or no consensus regarding efficacy exists.

Appendix B: The Lewisham Isolation Priority System: Scoring Grid and notes (reproduced from Masterton *et al.*[219])

CRITERIA	CLASSIFICATION	SCORE	COMMENTS
ACDP category	2	5	
	3	10	
	4	40	
Route	Air-borne	15	
	Droplet	10	
	Contact	5	Includes faecal-oral transmission
	Blood-borne	0	
Evidence of transmission	Published evidence	10	
	Consensus or high likelihood	5	
	No consensus or unlikely	0	
	No evidence	-10	
Significant Resistance	Yes	5	Such as MRSA, GRE, *etc.*
	No	0	
High Susceptibility of other patients with serious consequences	Yes	10	Specific for various infections and patient populations
	No	0	
Prevalence	Sporadic	0	
	Endemic	-5	This reflects the burden of infection in the hospital and cohort measures are more applicable
	Epidemic	-5	See above
Dispersal	High risk	10	Only for contact and droplet transmission, *e.g.* eczema, faecal incontinence, tracheostomy, *etc.*
	Medium. risk	5	
	Low risk	0	
TOTAL SCORE			

Appendix B concluded

Category of priority for isolation	Score
Low	0 – 20
Medium	21 – 39
High	40 – 50

1. Advisory Committee of Dangerous Pathogens (ACDP) Classification of Pathogens: The ACDP classification provides an acknowledged system of classifying organisms based on their transmissibility, pathogenicity and our ability to protect against or treat individual infections.

2. The probable route of transmission: Air-borne infections are those likely to spread readily if not isolated; blood-borne infections are least likely to do so.

3. Evidence for transmission: Although (1) and (2) may suggest transmission, the emphasis placed on evidence-based medicine now supports a requirement to demonstrate that transmission of specific infections has indeed occurred in hospitals.

4. Occurrence of infection in the hospital: The incidence or prevalence of an infection/colonisation in a hospital is frequently a consideration when deciding whether or not to isolate a patient. In a sporadic infection, isolation of a patient will have a higher priority than in an endemic or epidemic situation.

5. Antibiotic resistance: Emergence of antibiotic resistant bacteria is one of the principal causes for the increased demand on isolation facilities.

6. Susceptibility of other patients: When deciding whether or not to isolate a case, the presence of a susceptible patient population promotes the isolation of the potential source of sepsis.

7. Dispersal characteristics of patient: Whilst transmissibility of various infections have been addressed in 1, 2, and 3, it is well recognised that for a given infection certain patients present greater transmission hazards than others.

Appendix C: Full article appraisal criteria from Cooper *et al.*[197] (chapter 3, page 19)

For each article, the reviewers were first required to answer the following questions:

1. Is this a report of an MRSA outbreak or endemic MRSA?
2. Is it a hospital setting?
3. Is an isolation strategy or policy mentioned?
4. Is there a relevant outcome in the form of MRSA transmission data for patients (including colonisation or infection with MRSA)?

If the answer to any of these questions was 'no', the paper was rejected.

Appendix D: The Charlson Comorbidity Index[280]

Charlson Index			
Factor	**Weight**	**Tick**	**Score**
Myocardial Infarct	1		
Congestive heart failure	1		
Peripheral vascular disease	1		
Cerebrovascular disease	1		
Dementia	1		
Chronic Pulmonary Disease	1		
Connective Tissue Disease	1		
Ulcer disease	1		
Mild liver disease	1		
Diabetes	1		
Hemiplegia	2		
Moderate or sever renal disease	2		
Diabetes with end organ damage	2		
Any tumour	2		
Leukaemia	2		
Lymphoma	2		
Moderate or sever liver disease	2		
Metastatic solid tumour	6		
AIDS	6		
		Total Score	

Notes:

MI & CCF – documented diagnosis
PV disease – intermittent claudication, bypass for arterial insufficiency, gangrene, Acute AAA or thoracic aneurysm $\geq$ 6cm
Cerebrovascular disease = CVA with minor or no residue, TIAs
Diabetes – end organ damage = retinopathy, neuropathy or nephropathy
Renal – dialysis, post transplant, or serum creatinine > 3 mg% (265 µmol/L)
Liver disease – Mild = chronic hepatitis or cirrhosis, moderate or severe includes portal hypertension/ variceal bleeding.
Lymphoma – includes Hodgkin's, lymphosarcoma, Waldenstroms macro-globulinaemia, myeloma and other lymphomas.
Leukaemia acute & chronic myeloid and lymphocytic and polycythaemia vera.
Tumour – last 5 years
Connective tissue disease – Lupus, polymyositis, mixed connective tissue disease and moderate to severe RA

Appendix E: The Leeds Teaching Hospitals NHS Trust policy for the infection control management of MRSA

The Leeds Teaching Hospitals NHS
NHS Trust

LTHT Infection Control Policies

MRSA

"MRSA" stands for Methicillin Resistant *Staphylococcus aureus;* it is a bacterium that is resistant to certain antibiotics including flucloxacillin and all cephalosporins. MRSA is not a significant risk to healthy people, including health care workers and visitors, but can cause serious infection in vulnerable patients. Such infections can be very difficult and expensive to treat.

This policy covers the majority of situations in which patients with MRSA have to be managed. However some specialist units and areas within the LTHT will have specific arrangements that have been agreed with the Infection Control Team. A copy of these arrangements should be kept in the Infection Control Manual on the wards/department concerned.

Key Points

- Hand hygiene is the most important measure in preventing the spread of MRSA.
- Infection control management of patients with MRSA must be based on an assessment of the risk of spread to other patients.
- Patients who present an increased risk of spreading MRSA will need to be managed in Source Isolation. (See LTHT Source Isolation Policy).
- Patients admitted with a history of MRSA colonisation/ infection may need to be admitted into a single room, particularly if signs of clinical infection (i.e. risk of spread of MRSA to other patients).
- Equipment and the hospital environment can be involved in spread of MRSA if cleaning or decontamination is inadequate.

- Screening for MRSA will only be carried out, after arrangement with the Infection Control Team.
- Topical agents to reduce MRSA carriage may be used in certain patient groups or following advice from Infection Control.
- MRSA colonisation or infection should never be a contraindication to nursing or residential care discharge.

Where is MRSA found?

MRSA, like other *Staph. aureus* strains, colonises moist or broken skin, in particular the axillae and groin areas. The most common carriage site of MRSA is the nose; it can also be found occasionally in the throat. MRSA can cause a wide variety of infections including skin and wound infections and bacteraemia.

How does MRSA spread?

- MRSA is most commonly spread on the hands of health care workers.
- Hospital equipment can be a route of spread if not adequately decontaminated between patients. (See LTHT Decontamination of Hospital Equipment Including Medical Devices)
- Patients with MRSA are likely to contaminate inanimate objects and the hospital environment in their vicinity. Subsequently this contamination can be transferred to other patients either directly, or via staff hands.

What do you do if a patient is found to have MRSA?

Infection control management of patients from whom MRSA has been isolated must be based on **risk assessment**. (This is the assessment of the risk of MRSA being spread from such patients to others and the risk MRSA acquisition to those patients).

Staff caring for the patient should undertake the risk assessment. **Help and advice is available from Infection Control/Microbiology.**
The factors that need to be taken into account when assessing the risk of transferring MRSA to other patients include:

- The site or specimen from which MRSA has been isolated (e.g. wound swab, sputum etc).

- Whether the patient has clinical evidence of an infection (i.e. has associated symptoms) or is colonised (i.e. is asymptomatic).
- The environment in which the patient is being managed (i.e. the susceptibility of other patients to MRSA infection).

Examples of higher risk include: leaking wounds, drains in situ, exfoliating skin problems and coughing and expectorating patients (in sputum MRSA positives).

Part of the risk assessment includes the assessment of the risk of untoward outcome, to other patients. For this reason we can categorise patient areas into the following:

Hospital wards and departments can be broadly divided into 3 categories;

1. **High risk** – Critical Care areas eg ICU's, HDU, SJUH Liver Unit, Bone Marrow Transplant Unit, Renal Units, Orthopaedic and Vascular surgery.

2. **Medium risk** – "surgical" in-patient wards e.g. G. I. surgery Oncology/Haematology wards

3. **Low risk** – general "medical" or Care of the Elderly wards and outpatient areas. (Low risk does not mean **no** risk, advice on management of patients in these areas will be given by Infection Control/Clinical Microbiology).

Depending on the outcome of the risk assessment the patient will either need to be in Source Isolation (see Source Isolation Policy) or may be managed using Universal Infection Control Precautions (see Universal Infection Control Policy).

Examples of risk assessments (NB these are only examples - every case will need individual assessment)

1. A patient with MRSA in sputum who is coughing and expectorating would present a high risk of transferring the organism to others and will need to be isolated in any acute care environment.
2. A patient with MRSA in urine who is not catheterised, is continent and has no symptoms is very unlikely to present a risk to others and would not need isolating except in very high risk areas e.g. ICU.
3. A patient who has a superficial wound infection which is leaking slightly and requires dressing presents a moderate risk to others and may be isolated depending on the care environment e.g. isolation would be

required in a "surgical" or critical care environment but not necessarily in a "medical" environment.

What about ending source isolation?

- The decision to discontinue source isolation will be made using the same principles of risk assessment as described above i.e. as the circumstances of the patient, the infection or colonisation or the environment change, the need for continuing isolation will need to be re-assessed. For example a patient with a previously leaking wound that has now dried up may no longer require source isolation.

- Screening swabs/cultures for MRSA status play little or no role in such decisions **and should <u>not</u> therefore be undertaken routinely**.

<u>The Infection Control Team is available to discuss, and assist with risk assessment.</u>

Are there any specific precautions for MRSA?

- Most of the necessary precautions for managing patients with MRSA can be found in the Source Isolation, Universal Infection Control Precautions and Hand Hygiene policies. As with all patients the most important infection control procedure is hand washing and/or use of an alcohol hand rub.

- Additional measures may be required for certain patients e.g. specific peri-operative prophylaxis. These or similar strategies should not be attempted without prior discussion with Infection Control Team or Clinical Microbiologist.

Should any topical preparations be used to reduce the carriage of MRSA?

- In certain circumstances it will be necessary to try and reduce carriage of MRSA using topical agents (i.e. "Mupirocin" nasal ointment and "Aquasept" bathing).

- The topical control regimen (see appendix A.) should be used in patients in whom MRSA is isolated in the following areas:

1. Patients should be placed on the topical control regimen on admission if admitted to general adult ITU/Neuro ITU and general surgical HDU. The following criteria will be applied to identify those patients who require the topical control regimen:

    - **Patients age 65 years and over.**
    - **Patients who have had surgery or trauma this admission.**
    - **Patients who have known MRSA in the past.**

As previously stated part of the risk assessment includes the assessment of the risk of untoward outcome, to other patients. For this reason we can categorise patients on ITU/Neuro and general surgical HDU who are neutropaenic or admitted from a haematology or oncology unit as high risk. These patients should also receive the topical regimen (see appendix A) to reduce potential acquisition.

2. In all Renal, Liver, Haematology, Orthopaedic, Vascular surgery and Cardiothoracic surgery wards, GI surgery and ENT surgery, the topical control regimen should be commenced if MRSA is found on a clinical specimen.

3. Additional measures may be required for certain patients' e.g. specific peri-operative prophylaxis. These or similar strategies should not be attempted without prior discussion with Infection Control / Clinical Microbiologist.

4. Patients **should be given one course only of the topical control regimen per LTHT in patient stay**. (This includes all previous use including prophylaxis use.) If you require advice please contact Infection Control/Clinical Microbiologist. This issue is important in minimising the risk of emergence of resistance to mupirocin.

Should patients be screened for MRSA?

Screening for MRSA will be carried out, **ONLY** after arrangement with the Infection Control Team.

hat about admitting a patient who is known to have, or ve had MRSA?

Patients who have had MRSA in the past are likely to remain colonised and may present a risk of infection to others.

If a patient is admitted from home or another health care provider with known MRSA (or a history of MRSA). A risk assessment should be undertaken as soon as possible and the patient managed accordingly. If no single room is available a risk assessment should be undertaken and the patient managed using Universal Precautions and Source Isolation around the bed space if appropriate. (Infection Control/Microbiology can be contacted for advice).

If patients are transferred within the LTHT, the ward/area who are transferring the patient must discuss the risk assessment and management of the patient with the receiving ward.

'hat measures are needed on discharge?

If the patient is to be discharged to the care of a nursing, residential home or district nurse then a copy of the community discharge sheet [see appendix B] should accompany the patient.

Colonisation/ Infection with MRSA should **never** be a contraindication to nursing home/residential care.

If the patient is being transferred to another hospital trust/health care provider the management of the patient should be discussed with the receiving facility before the patient is transferred.

References and Further Reading

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olicy Date: September 2001

eviewed Date: February 2004

eview Date: February 2006

Appendix A]: Topical Regimen for the Control of MRSA Carriage

pirocin 2% nasal ointment (Bactroban)

y with a cotton wool swab or finger to the nasal nares 2 times per day for 5 days. Wash and dry hands thoroughly before and after each application.

iseptic body wash

:

closan 2% (Aquasept)

ieous Povidone Iodine (Betadine) skin cleanser 4%

orhexidine gluconate 4% (Hibiscrub)

ly for 5 days.

maximum effect these products should be used neat as a liquid p/shampoo.

ctions for use (also see individual product directions)

Wet skin before application.
Using as a liquid soap/shampoo, apply the chosen product from head to toe.
Wash vigorously with particular attention to the groin/axilla regions.
Rinse thoroughly.
Dry, using clean towels.

ier topical agents may be required but the following should only be used equested by Infection Control/Microbiology.

iseptic powder (Sterzac or CX powder)

ly like talc following bathing, especially to axilla and groin areas.

rsodyl mouthwash

the mouthwash 4 times per day. If present, dentures must be removed and cleaned using mouthwash.

ppendix B]: Guidelines on the Control of *Staphylococcus aureus* (including MRSA) in Patients Discharged from Hospital.

ıitions

Colonisation: when bacteria that are able to cause infection are isolated from a non-infected site, e.g. *Staphylococcus aureus* in the nose.
Infection: is the reaction to microbes lodging and multiplying in the tissues, e.g. abscesses, wound infections or chest infections.

ɔugh these guidelines are to be used with patients discharged with an infection, we may not ys be aware of colonisation or even infection. Therefore, constant good practice. cularly hand hygiene, is necessary to prevent the spread of microbes.

vidual assessment

y suspected infected patient should be assessed so that their treatment can be determined ıe relevant medical staff, in conjunction with the microbiologist.

dwashing

essary after contact with infected people or contaminated articles: paper towels must be l to dry hands. Alcohol handrub should be available, and its use understood.

tective clothing

gle-use seamfree gloves should be used for handling contaminated dressings, linen, ıpment etc. Single-use plastic aprons to be used for close contact with infected persons or r immediate environment.

ation

usually needed outside hospital.

ptic technique

be used when dealing with wounds and for other aseptic procedures.

ste

ected materials, e.g. dressings, to be disposed of as clinical waste.

ıen

low usual laundry procedures.

ucation and prevention

ff should apply universal infection control precautions to all patients.

mmunication

transfer or discharge, advice about any infection should be included in the information en to other providers of health care.

pendix F: The Leeds Teaching Hospitals NHS Trust policy for source lation

The Leeds Teaching Hospitals NHS
NHS Trust

LTHT Infection Control Policies

Source Isolation

ırce isolation is the physical separation of one patient from another, in order to vent spread of infection. Universal Infection Control Precautions must be ;erved at all times with all patients, including those in isolation.

1. How do you decide when isolation is needed?

The decision to isolate a patient should be based on the infection risk, and taken preferably after discussion with the Infection Control Team.

A risk analysis approach should be carried out. For example, patients with poor hygiene are more likely to cause cross-infection.

Isolated patients may experience more anxiety and depression. Isolation may hamper rehabilitation. To reduce these risks, preparatory information should be given wherever possible:

- Explanation of the nature of disease or organism, symptoms and treatment.
- Control methods and their rationale with advice for patients regarding their responsibility and their adoption of correct measures.

Regular assessment and evaluation of the situation, in conjunction with the Infection Control Team is necessary to decide if isolation of the patient remains the most appropriate form of care.

The patient must be nursed in a single room with a wash basin and preferably an en-suite toilet. If an en-suite toilet is not available, a commode for sole use of the isolated patient should be kept in the isolation room for the duration of the patient's stay.

Ensure the isolation room door is closed at all times apart from necessary entrances and exits, when airborne infection risk is present.

Limit the number of staff entering the isolation room. Reducing the number of staff who come into contact with the patient will further reduce the risk of spreading the infection.

If isolation is for a childhood diseases (i.e. infections such as measles, mumps, rubella, for which routine vaccination occurs, or chicken pox), it is preferable that only staff who are immune to the disease attend to the patient (see specific guidelines, or if necessary, discuss with the Infection Control Team).

2. How to prepare the room.

Make sure that all unnecessary equipment and furniture are removed from the room, this will facilitate cleaning and limit the items, which may become contaminated.

It is important that the equipment in the room is dedicated to the isolated patient.

Do not overstock the room, as equipment that cannot be cleaned will be disposed of.

All personal belongings and equipment should be washable, cleanable or disposable.

Discourage the patient from keeping unnecessary belongings in the room, but remember the need for psychological care of the patient whilst he/she is in isolation.

Place isolation sign on the door (see appendix). The sign is designed to inform anyone intending to enter the room of the situation, but not label the patient as being infectious.

Set up a trolley/table/shelf outside the room with single use gloves and aprons. Ensure that alcohol hand rub/gel is available within the constraints of COSHH.

Keep charts and kardex **OUTSIDE** the room to reduce the risk of contamination.

- Make sure the hand wash basin is stocked with appropriate hand hygiene product (discuss with the Infection Control Team if necessary) and paper towels.

- Place yellow clinical waste bag, sharps bin, red linen bag, and alginate liner in the room.

3. How to care for the patient

- Universal precautions must be used at all times.(please see LTHT universal precaution policy)

Hand hygiene

- Strict and thorough hand washing is mandatory after any direct contact with the patient or his/her immediate environment e.g. bed making, moving the patient, cleaning etc. Don't forget to cleanse hands after removing gloves.

- Soap and running water is adequate for hand hygiene, alcohol hand rub/gel should be used as a supplement once outside the room. (See Hand Hygiene Policy)

- Encourage the patient to cleanse their hands before eating and after going to the toilet.

Protective clothing

- Wear single use gloves for direct patient contact, contact with body fluids, potentially infectious material or when touching items in the environment which may be contaminated.

- Wear single use plastic apron for close patient contact (e.g. bed bathing, moving patient), when in close contact with potentially infected material (e.g. bed making), and any other situation when contamination of clothing may occur.

- Remove apron, then gloves and discard promptly into yellow clinical waste bag. Wash and dry hands thoroughly after having removed protective clothing and before leaving the isolation room. Use the alcohol hand rub/gel out side the room.

- Except in certain circumstances there is little evidence that the use of masks contributes to preventing cross infection. If in doubt, discuss with the Infection Control Team.

- Protection of eyes, nose and mouth may be necessary if blood/body fluid sprays or splashes are possible. The following options are available: safety spectacles, goggles, masks and visors. Visors usually offer the best protection.

Disposal of body fluids, waste and linen

- Dispose of all excreta promptly, preferably by discarding it directly into the bedpan washer/macerator or the patient's own toilet.

- Use protective cover for bedpans/urinals/vomit bowls when transporting to the sluice room.

- Protective clothing used within the isolation room may be worn to the sluice room, but discarded immediately into yellow clinical waste bag after disposal of excreta.

- Ensure thorough and frequent cleaning of the commode/toilet using sanitiser.

- Deal with any blood/body fluid spillage immediately, wearing appropriate protective clothing and disinfecting the spillage with 10,000 ppm chlorine releasing solution.

- Place waste contaminated with blood/body fluids directly into the yellow clinical waste bag in the isolation room. As soon as these bags are 2/3 full the bags must be tied in a swan neck and a tag attached indicating place of origin. The bags must be removed from the room to the waste storage area and a new yellow clinical waste bag placed in the isolation room.

- All linen within the isolation room must be placed into red alginate bags and red linen bags for safe transportation to the laundry. This includes unused linen when the room is no longer required for isolation purposes.

- Double bagging of clinical waste and linen is unnecessary, as studies have shown that the outer surface of the bags does not become significantly contaminated.
- Place all disposable sharps in the sharps bin immediately after use.

Crockery/cutlery

- All crockery/cutlery must be decontaminated in a dishwasher with a final rinse temperature of 80°C.

- Washing by hand is inadequate without a final rinse for one minute at 80°C.

- Disposable crockery and cutlery should not be used.

Bathing

- To reduce the risk of cross-infection, patients with infections must be bathed last.

- Always clean the bath with sanitising powder after any patient has used it, this method of disinfection is fine after infected patients.

- Showers may be used and the same criteria as above used.

Dressings

- All wounds should be dressed in the isolation room using aseptic technique.

Cleaning

- The Infection Control Team will advise on the frequency of cleaning the isolation rooms and solutions to be used.

- The nurse in charge must inform the locality supervisor of the need for isolation cleaning.

- The vacated bed, mattress and bed area on the ward must be thoroughly cleaned before it can be reoccupied.

- Make sure that separate cleaning equipment is being used to clean the isolation rooms. **This equipment must be kept clean and dry within the room. The mop head must be removed and sent to the laundry after each use**.

- Isolation rooms should be cleaned last, after other rooms, bays and general areas on the ward

- Single use gloves and aprons must be worn when cleaning the isolation rooms and hands washed before leaving the room.

- Special attention must be given to all horizontal surfaces and frequently touched surfaces, such as door handles/door push plates,nurse call system, toilet areas and sink taps.

- A thorough terminal clean must be done when the room is no longer required for isolation purposes. Curtains and walls need only be washed if visibly soiled.

Investigations/visits to other departments

- Ideally, investigations should be performed in the isolation room.

- If visits to other departments/wards are unavoidable, please contact the Infection Control Team.

- The receiving department should also be contacted to ensure that adequate precautions are taken.

- In principle the patient from the isolation room should be last on the list to minimise contact with other patients. The same precautions taken on the ward should be carried out in the department.

Transfers to other wards/health care institutions

- These should only take place if unavoidable, please discuss with the Infection Control Team.

- The receiving ward must be informed and a single room arranged.

- The Infection Control Team will inform the relevant Infection Control Nurse about the transfer.

- The patient's health should take priority over the infection problem; e.g. if the patient is required to be transferred to ITU or CCU.

In the case of death

- In order to protect the mortuary staff; follow the LTHT policy for handling deceased patients with known infection.

4. What about visitors/parents/carers?

- Explain the reason for isolation, maintaining confidentiality at all times, (if available, give information leaflet on specific infection)

- Advise on hand hygiene and/or other precautions. Encourage visitors not to have contact with other patients on the ward.

- Visitors need only wear protective clothing if they are going to have close contact with the patient, eg. helping with patient's physical care, or if otherwise advised.

- Discuss with the Infection Control Team, or see specific disease policy to ascertain if visitors should be excluded due to particular susceptibility.

5. When can isolation precautions be stopped?

- When the patient is no longer at risk of spreading infection to others.

- Frequent assessment and evaluation of the patient's situation is therefore important.

- Some specific disease policies give criteria on when isolation precautions can be stopped.

- If in doubt, discuss with the Infection Control Team.

- Make sure the vacated room is thoroughly cleaned. Use the same solutions and equipment that have been used for isolation cleaning. All equipment and belongings must be cleaned before being brought out of the room or used again. Any unused disposable items, which may be contaminated and cannot be cleaned, must be disposed of.

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Policy Date: **June 2000**
Revised Date: **April 2003**
Review Date: **April 2005**